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MONKEYPOX: A WAKE-UP CALL TO END NTDs

As Monkeypox spreads globally, another neglected tropical disease (NTD) of the poor gets attention only after it infects people in wealthy countries. Monkeypox is not new. It has been regarded as a neglected tropical disease of Western and Central Africa since the early 70s, causing illness and death for decades.

Shaping the future of healthcare

SIEMENS Healthineers

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September 2022

Photo credit: RTI International/Louise Gubb

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Tanzania school-based MDA Students in the Lindi region of Tanzania receive medicines for NTDs during a school-based mass drug administration.

“ We have been working on monkeypox in Africa for several years, but nobody was interested. Once monkeypox was detected on other continents, ‘the world reacted.’ It was the same with the Zika virus and we have to stop this discrimination.”

—Ibrahima Soce Fall, WHO Assistant Director General for emergencies

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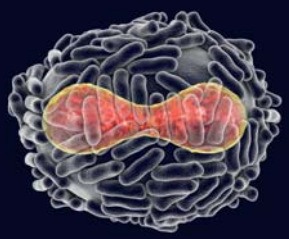

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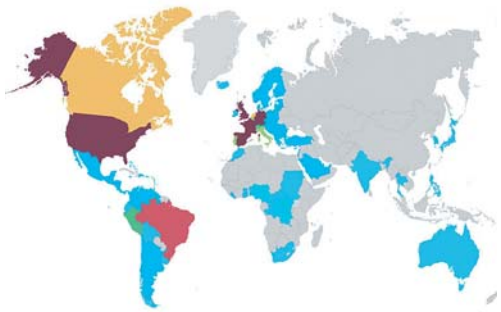

Feature

IN EVERY ISSUE

ON THE COVER

Cover Styling: **V K Haris**

GO GREEN

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Prologue

Today's NTD could be tomorrow's pandemic

As I pen this message, the world is on a gentle pause to the new outbreak, viz. monkeypox. The media, since May 2022, has reported around 53000 cases of monkeypox across 102 countries, and 18 deaths from this. Notably, most of these cases have been reported in geographies where monkeypox has not been endemic. The WHO had been concerned enough to declare the current monkeypox outbreak a Public Health Emergency of International Concern (PHEIC).

This was on July 23, 2022, and the highest alarm the U.N. agency could sound. Meanwhile, the number of cases in the U.S. had crossed the 10,000 mark by mid-August 2022, and the Biden administration declared a national health emergency. During the week of 29 August to 4 September 2022, the number of cases reported in the regions of Europe and America declined compared to the week of 22 to 28 august, driving the observed global decrease. On 25 August, WHO updated the interim guidance on Surveillance, case investigation, and contact tracing for monkeypox with the latest information on symptomatology and epidemiological parameters, and to align with the Temporary Recommendations issued by the Director General, after the declaration of the Public Health Emergency of International concern (PHEIC). The External Situation Report 5, published 7 September 2022 by the WHO places the global risk at moderate, but the regional risk for the European region is still on high as we go to press.

Before monkeypox announced its silent but far-reaching arrival in Europe and the U.S., nobody seemed to care because it was confined to Africa, where it is endemic. Global public health partners did not give it much attention to the point that it became one of the neglected tropical diseases (NTD).

There are 20 infections and conditions under the umbrella of neglected tropical diseases caused by bacterial, parasitic, or viral infections, and they often result in disability, cognitive damage, disfigurement, or death.NTD affects more than 1.7 billion people worldwide, predominantly in tropical and subtropical areas among the most vulnerable, marginalized populations.

NTDs are considered neglected for many reasons, including lack of awareness and their global rejection as important public health matters. "Neglected" is also a word that aptly describes how low-income populations affected by these diseases have been left to fend for themselves.

Ending NTDs is not some utopian fantasy; it's a tangible vision of the future we can work toward every day. The World Health Organization (WHO) has outlined an ambitious roadmap to tackle these diseases by 2030, but carrying it out requires countries, partners, and Global Citizens to demonstrate strong political will.

The monkeypox is a wake-up call. Today's NTD could quickly escalate into tomorrow's global outbreak or a pandemic.

Dr Azad Moopen, MD, FRCP
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Case Reports

Editorial

NTDs: Avoid Further Neglect!

This is my maiden editorial for *Aster Medical Journal* (AMJ).

I know that being an editor of a scientific journal is a challenging task amidst clinical practice. I am fully conscious of the commitment of my predecessors in this office in curating each edition of the Aster Medical Journal – they have identified good science and shared it with the scientific communities responsibly.

Their outstanding job over the years has set a standard of excellence that is difficult to improve. Their dedication has transformed AMJ into a journal of the highest quality, with engaging articles, wide acceptance, and an appreciative readership. I put on record my gratitude for their entrusting me with this legacy.

As I am writing this editorial, I read how the head of the World Health Organization shifts to a more upbeat tone while urging countries to keep working to control the virus.

"We have never been in a better position to end the pandemic," WHO Director-General Tedros Adhanom Ghebreyesus said in a briefing with journalists. "We are not there yet, but the end is in sight." Fewer deaths were linked to Covid around the world last week than at any time since March 2020, said Dr. Tedros.

While we see the end of a pandemic, this issue of Aster Medical Journal brings a different perspective and looks at NTDs or Neglected Tropical Diseases, which could potentially escalate into epidemics, and we have in perspective the global outbreak of monkeypox.

The feature article in this will keep you abreast of surgical robots by raising the most pertinent question - is it time to hand the surgeon's scalpel to a robot?

This issue also brings you an array of clinical cases and an insightful review article on exosomal biomarkers for neurologic conditions.

I hope you will find this issue of AMJ worth reading, and I look forward to your support and feedback to take AMJ to newer summits and standing.

Happy Reading.

Dr Geetha Philips, MD, FRCP

Reports of "tomato flu" outbreak in India are not due to new virus, say doctors

BMJ has reported that a "new" virus known as tomato flu reported in India is a variant of the already endemic hand, foot, and mouth disease (HFMD), doctors have confirmed. A letter published in *Lancet Respiratory Medicine* on 17 August reported the emergence of the "new" virus in the Indian state of Kerala in children younger than 5. It said that as of 26 July, more than 82 children aged under 5 had been reported by local government hospitals, to have had the infection. One of the predominant symptoms of the disease is the presence of tomato-like red welts all over the body, particularly the hands, feet, and oral cavity. These are accompanied by symptoms very similar to those of covid-19, such as fever, fatigue, and body aches. Lancet notes that similar to other types of influenza, tomato flu is very contagious and children are at increased risk of exposure to tomato flu as viral infections are common in this age group and spread is likely to be through close contact.

Warning label most effective in identifying harmful nutrients

A new study in India has found that warning labels on food packets are most effective in helping consumers identify foods high in sugar, saturated fat and sodium as compared to other labelling formats.Published in open access journal *Nutrients* earlier this month, the study is the first peer-reviewed paper on the subject in an Indian context. It found that on most parameters, the Health Star Rating (HSR) format—where a product is assigned between 1/2 a star and five stars—was least effective. The study comes at a time the Food Safety and Standards Authority of India (FSSAI) is expected to issue its draft regulation on front-of-package labelling (FOPL) and has indicated that it favours HSR, earning the ire of public health experts who have accused it of favouring the food industry.

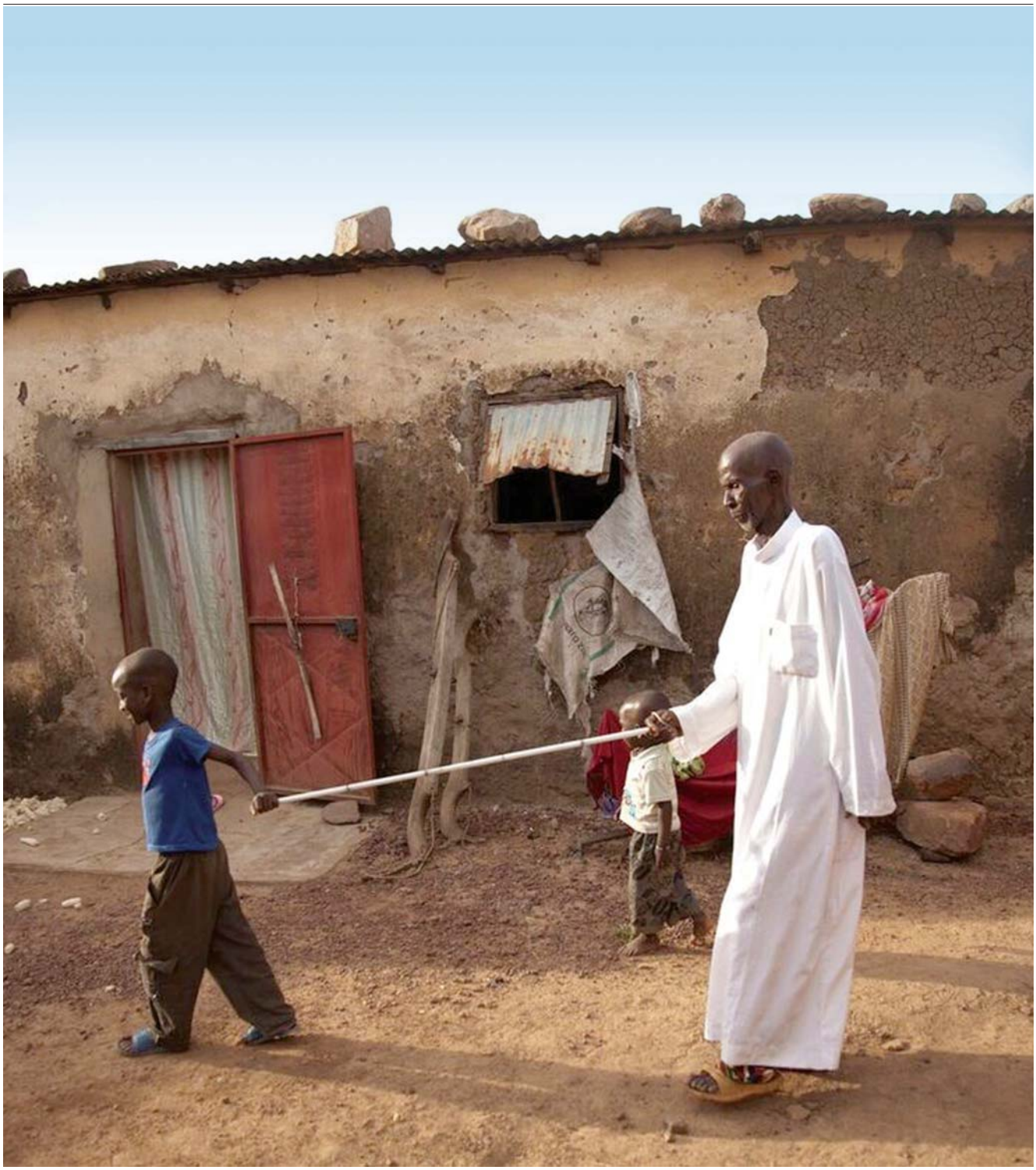
The authors conducted an in-person randomised experiment on 2,869 adults in six states in India, where participants were shown food packets with one of five FOPLs—a control label (barcode), nutrient-specific warning label (octagon symbol indicating whether the product was high in salt/sugar or saturated fat), Health Star Rating, guideline for daily amount (GDA that gives nutritional content information) or traffic light label (indicating red, amber or green levels of nutrients of concern). The objective of the study was to evaluate the impact of different labels in helping consumers correctly identify packaged products containing excess levels of nutrients of concern such as sugar, saturate fat and sodium.

Scotland becomes first country to make period products free for all

The Scottish government said it became the first in the world to legally protect the right to access free period products when its Period Products Act came into force Monday . A law has taken effect in Scotland to ensure period products are available free of charge to anyone who needs them.

Under the new law, schools, colleges and universities as well as local government bodies must make a range of period products available for free in their bathrooms. The Scottish government already invested millions of pounds since 2017 to fund free period products in educational institutions, but the law makes it a legal requirement.

The brief



© Photo: **WHO**

Malian Moce lost his eyesight over thirty years ago to river blindness. More than 200 million people globally require treatment for the disease, one of the leading causes of preventable blindness. The UAE began its Reach initiative mainly to help eliminate river blindness and lymphatic filariasis, which are caused by parasitic worms carried by flying insects.

by **Daniel Bardsley**

Sheikh Mohamed bin Zayed's mission to help eradicate tropical diseases

Long-running campaign has pledged millions of dollars to tackling crippling, preventable conditions such as Guinea worm and river blindness.

Among the humanitarian causes that UAE President Sheikh Mohamed bin Zayed has long shown a commitment to is the eradication of tropical diseases.In the fight against neglected tropical diseases, such as Guinea worm disease, a parasitic infection that mostly affects poor communities in Africa, Sheikh Mohamed has provided both advocacy and generous financial assistance.

The new president's efforts follow those of his father, Sheikh Zayed bin Sultan, who decades ago began supporting the Carter Centre, an organisation founded by Jimmy Carter, the former US president, that fights tropical illnesses.

At the beginning of 2021, Sheikh Mohamed pledged to give $10 million to the centre to mark the 30th anniversary of its partnership with the UAE. "In the UAE, we have seen first hand the vital link between health and prosperity, and we remain steadfast in our vision of a world where every person deserves to live a healthy, dignified life," Sheikh Mohamed said at the time.

Sheikh Mohamed bin Zayed presents a reach award to Abdullah Khalifa Al Ghafli during the Global Health Forum. Seen with Bill Gates. Hamad Al Kaabi / Crown Prince Court - Abu Dhabi

Indeed, the UAE has, since 2010, donated more than a quarter of a billion dollars in the fight against preventable tropical diseases such as Guinea worm. Already significant progress has been made to eliminate Guinea worm disease, with the annual tally of cases falling from 3.5 million in 1986 to just 14 last year. Thanks to the Carter Centre and its partners, supported by Sheikh Mohamed, the hope is that Guinea worm disease will be eliminated entirely.

But even if that happens, the work is set to continue, because neglected tropical diseases are thought to still cause as many as 170,000 preventable deaths annually. As well as causing fatalities, these diseases keep some of the world's poorest communities poor by stopping adults from working and children from attending school.

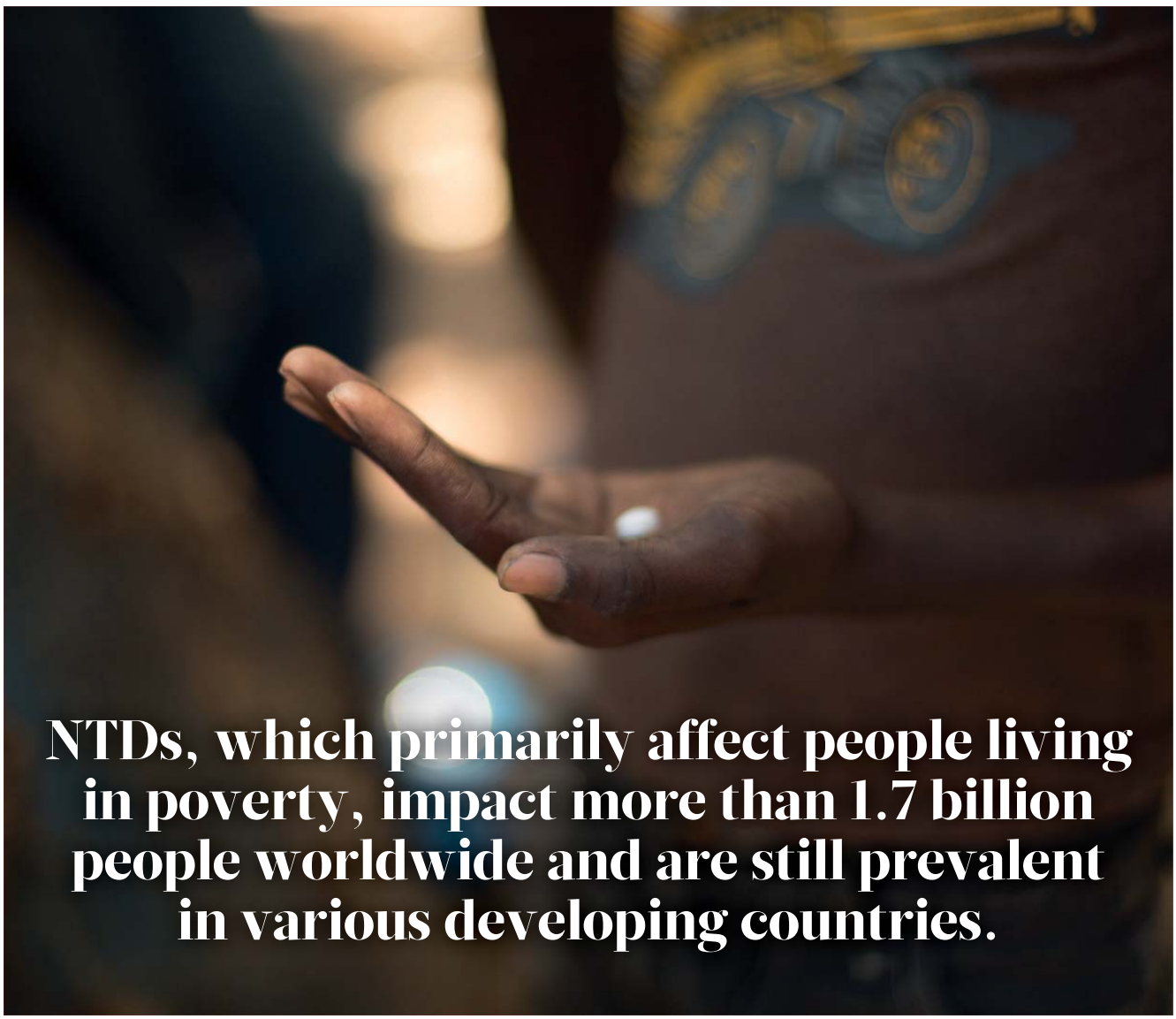
One of Sheikh Mohamed's biggest contributions to combating tropical diseases was his setting up, in 2017, of the Reaching the Last Mile Fund, a decade-long $100m initiative that aims to eliminate river blindness and lymphatic filariasis in a number of African countries. Among the supporters of the fund is the Bill and Melinda Gates Foundation. In December Mr Gates, the Microsoft founder and the foundation's co-chair, visited the UAE and was received by Sheikh Mohamed, and the two men discussed the fight against diseases.

After the meeting, Sheikh Mohamed hailed on social media an announcement by the African nation of Niger that it had eradicated river blindness as "a milestone in the fight against neglected tropical diseases".

"Through initiatives such as the Reaching The Last Mile Fund, we remain committed to working with our partners to support these crucial global efforts," Sheikh Mohamed said. Sheikh Mohamed also has a long-term commitment to combating malaria, pledging millions of dollars to help prevent the mosquito-borne condition.

On World Malaria Day, which fell on April 25, Sheikh Mohamed said it was important to use innovation to reduce the burden of preventable disease."We remain committed in the fight to end malaria through global partnerships and will continue to work with the global community to lead on innovative and equity-driven programmes to save millions more lives," he said last month.

Monkeypox: A wake up call to end NTDs



NTDs, which primarily affect people living in poverty, impact more than 1.7 billion people worldwide and are still prevalent in various developing countries.

Photo credit: RTI International/Timothy La Rose

The term Neglected Tropical Diseases (NTDs) was coined in the early 2000s, to refer to a varied group of diseases that share two separate backgrounds: a social background (poverty) and a geographical background (tropical countries). Although the term NTD first brings to mind diseases like Malaria, Dengue, and perhaps Yellow Fever, the entire list covers 20 infections and conditions under the label, as included by the WHO. The international agency for global health defines NTD as a diverse group of conditions that are prevalent in tropical areas, mostly affecting impoverished communities and disproportionately affecting women and children.

NTDs are caused by bacterial, parasitic, or viral infections, and they often result in disability, cognitive damage, disfigurement, or death. Though the epidemiology of these diseases is "complex," they tend to thrive in remote parts of the world where access to sanitation, nutrition, and health care is lacking. These diseases have caused devastating health, social and economic consequences to more than 1.7 billion people worldwide. The epidemiology of NTDs is complex and often related to environmental conditions. Many of them are vector-borne, have animal reservoirs and are associated with complex life cycles. All these factors make their public-health control challenging.

NTDs are considered neglected for many reasons, including lack of awareness and their global rejection as important public health matters. "Neglected" is also a word that aptly describes how low-income populations affected by these diseases have been left to fend for themselves. More than diseases, one could say its people who are neglected.

NTDs have held back human progress for long periods; limiting, weakening, and causing premature death, if left untreated. Yet NTDs still struggle to attract political prioritization and remain largely unknown and under-addressed. Africa alone bears approximately 40% of the global burden of NTDs. People living with NTDs often suffer an abysmal quality of life. Consider someone affected by intestinal worms, bilharzia (schistosomiasis) and trachoma. The children may regularly miss school, their caretakers may struggle to keep their jobs, and all may possibly be the target of societal stigmatization.

This brings the discussion to the current outbreak worrying Europe and the U.S, the monkeypox. But before monkeypox pronounced its silent but far-reaching impact in the West, the world was not hugely concerned about the illness. It was, till then, confined to Africa where it is endemic. The global public health partners were apprehensive that it had already been one of the NTDs of Africa.

There are health experts who contemplate the potential of what is happening now, as manifested five years ago, when the disease left its endemic zone. Professor Chris Beyrer from Johns Hopkins University, in his address at the International Aids Conference in Montreal, Canada, says this: "It turns out that monkeypox emerged out of its Central African endemic zone into West Africa in 2017, five years ago, and the outbreak has been ongoing for five years with no urgency, no response, no World Health Organization (WHO) engagement around vaccines in those countries".

Monkeypox was in fact first identified in humans in 1970 in the Democratic Republic of the Congo (DRC) in a nine-month-old boy, in a region where

Photo credit: **RTI International**

“ We have been working on monkeypox in Africa for several years, but nobody was interested. Once monkeypox was detected on other continents, ‘the world reacted.’ It was the same with the Zika virus and we have to stop this discrimination.”

—Ibrahima Soce Fall
WHO Assistant Director General for Emergencies

smallpox had been eliminated in 1968. Since then there have been sporadic cases in the Congo Basin - home to some of the largest tropical rainforests in the world, as well as in Benin, Cameroon, the Central African Republic, Gabon, Côte d'Ivoire, Liberia, Nigeria, Republic of Congo, Sierra Leone, and South Sudan.

The WHO Assistant Director-General for emergencies, Ibrahima Soce Fall mentions, "We have been working on monkeypox in Africa for several years, but nobody was interested." He added that once monkeypox was detected on other continents, "the world reacted". "It was the same with the Zika virus and we have to stop this discrimination”.

The eradication of NTDs is not a utopian fantasy; it’s a tangible vision of the future that we can work towards, every day. The World Health Organization (WHO) has outlined an ambitious roadmap to tackle these diseases by 2030, but carrying it out requires countries, partners, and Global Citizens to demonstrate strong political will. On 30 January 2012, pharmaceutical companies, donors, endemic countries and non-government organizations came together to sign the London Declaration on Neglected Tropical Diseases. Together, they committed to control, eliminate or eradicate ten diseases by 2020 and improve the lives of over a billion people.

The 2012 London Declaration, which encouraged unprecedented global action and progress in the fight against NTDs, officially expired in 2020.Even though the London Declaration has not met all of the targets, ample progress has been made and cases of some of the diseases that have plagued humanity for centuries, such as sleeping sickness and Guinea worm disease, are at an all-time low. In 2020, 600 million fewer number of people required interventions against NTDs than in 2010, and 42 countries eliminated at least one NTD. But controlling this diverse group of 20 conditions, which affect 20% of the world's population, will require attention to neglected populations, not just neglected diseases. The agenda to end NTDs has an important role in reducing poverty and prioritizing the needs and rights of underserved populations in countries across the income spectrum.

List of NTDs

Buruli ulcer
A debilitating mycobacterial skin infection causing severe destruction of the skin, bone and soft tissue.

Dengue and chikungunya
Two mosquito-borne, outbreak-prone viral conditions causing a flu-like illness that can be associated with severe, painful and disabling symptoms and, in the case of dengue, may cause shock, haemorrhage and death.

Echinococcosis
A disease caused by the larval stages of tapeworms forming pathogenic cysts in human organs, acquired by ingesting eggs most commonly shed in the faeces of dogs and wild animals.

Sleeping sickness
A protozoan infection spread by the bites of tsetse flies that is almost 100% fatal without prompt diagnosis and treatment to prevent the parasites from invading the central nervous system.

Leprosy
A complex disease caused by infection with a slow-growing bacterium, mainly affecting the skin, peripheral nerves and eyes.

Chagas Disease
A life-threatening protozoan illness transmitted to humans through contact with vector insects (triatomine bugs), ingestion of contaminated food, infected blood transfusions, congenital transmission, organ transplantation or laboratory accidents.

Guinea worm disease
A helminth infection transmitted exclusively by drinking water contaminated with parasite-infected water fleas; one year later, adult female worms painfully ulcerate through the skin, often of the legs, in order to expel their larvae.

Foodborne trematodiases
A group of infectious diseases acquired by consuming fish, crustaceans and vegetables contaminated with larval parasites; clonorchiasis, opisthorchiasis, paragonimiasis and fascioliasis are the most common.

Leishmaniases
A group of protozoan diseases transmitted through the bites of infected female sandflies; the most severe (visceral) form attacks the internal organs and in its most prevalent (cutaneous) form causes skin ulcers, disfiguring scars and disability.

Lymphatic filariasis
A helminth infection transmitted by mosquitoes and resulting in adult worms inhabiting and reproducing in the lymphatic system; it is associated with recurrent painful inflammation and abnormal enlargement of limbs and genitals.

On the tenth anniversary of the London Declaration on NTDs, at a pivotal event held in Kigali in Rwanda, governments, pharmaceutical companies, foundations, and NGOs committed to collaborate in their efforts to stop NTDs. Building on the progress of the London Declaration on NTDs and putting individuals and communities at the center of the NTD response, the signatories of this declaration came together to commit to ending NTDs by signing the Kigali Declaration on NTDs.

The Kigali Declaration is a high-level political declaration which aims to mobilize political will and secure commitments to achieve the Sustainable Development Goal 3 (SDG3) target on NTDs and to deliver the targets set out in the World Health Organization's Neglected Tropical Disease Roadmap (2021-2030).

However, without increased understanding of the economic burden these diseases place on countries, and greater action from local governments and national stakeholders, we will not see an end to the scourge of these diseases. NTDs need to receive higher priority on the national and global agenda, through processes such as regional/national strategic planning, domestic financing, and capacity strengthening for NTD programs—all aimed at ameliorating the quality of life for people living with these diseases.

Mycetoma, chromoblastomycosis and other deep mycoses
Chronic, progressively destructive inflammatory diseases of the skin and subcutaneous tissues which usually affect the lower limbs. People become infected when injuries break the skin and allow fungi (and bacteria in the case of mycetoma) to enter the body.

Onchocerciasis
A helminth infection transmitted by the bite of infected blackflies causing severe itching and eye lesions as the adult worm produces larvae eventually leading to visual impairment and permanent blindness.

Rabies
A preventable viral disease transmitted to humans through the bites of infected animals, especially dogs, that is invariably fatal once symptoms develop.

Scabies and other ectoparasitoses
A group of infestations of the skin caused by mites, fleas or lice; scabies occurs when the human itch mite burrows into the upper layer of the skin where it lives and lays its eggs, causing intense itching and rash.develop.

Schistosomiasis
A group of trematode infections acquired when larval forms released by freshwater snails penetrate human skin during contact with infested water; schistosomiasis is typically associated with liver and urogenital pathology.

Snakebite envenoming
A potentially life-threatening condition caused by toxins injected through the bite of a venomous snake, often responsible for acute medical emergencies. Envenoming can also be caused by having venom sprayed into the eyes by certain species of snakes

Soil-transmitted helminthiases
Helminth infections transmitted through soil contaminated by human faeces; they cause anaemia, vitamin A deficiency, stunted growth, malnutrition, intestinal obstruction and impaired development

Taeniasis and cysticercosis
Taeniasis is caused by adult tapeworms in human intestines; cysticercosis results when humans ingest tapeworm eggs that develop as larvae in tissues, including the brain (neurocysticercosis).

Trachoma
A bacterial infection transmitted through direct contact with infectious eye or nasal discharge, and associated with unsafe living conditions and hygiene practices; if left untreated, it causes irreversible corneal opacities and blindness.

Yaws
A chronic, disfiguring bacterial disease affecting mainly the skin and bone. Other endemic treponematoses similar to yaws are also considered NTDs

Source: **World Health Organization**

Fulfilling the new agenda will require a move away from siloed disease-specific approaches to cross-cutting efforts, including coordinated NTD programs and the integration of such programs into national health systems. The ambitious WHO NTD Roadmap 2021–2030 calls for infrastructure and the health-care workforce to be strengthened to ensure that patients can receive primary care, even in remote areas. There is also a demand for a One Health approach and stronger collaboration across sectors such as health, water, sanitation and hygiene, education, and food safety.

These changes will require a shift towards country ownership of NTD programs. Endemic countries will need to budget for and implement programs both within and beyond health. NTDs not only perpetuate cycles of poverty, but cost billions of dollars in health care and lost productivity, making a strong economic case for investment.

The COVID-19 pandemic has been an unprecedented setback to the NTD agenda. It has disproportionately made life worse for neglected populations, not only increasing poverty globally but also directly affecting NTD interventions. A WHO survey reported that NTD services have been frequently and severely impacted by COVID-19 and that disruptions occurred in 44% of countries. Modelling has

Photo credit: **RTI International/Louise Gubb**

shown that trachoma, schistosomiasis, and visceral leishmaniasis are the most affected NTDs, demanding the implementation of more intensive intervention strategies. Doing so will require a shift from one-size-fits-all approaches to innovative data-driven and targeted efforts tailored to local epidemiology, health systems, infrastructure, and resources.

However, according to the G-FINDER project, research and development for NTDs has been stagnant for decades, and receives far less funding compared with, for example, HIV, malaria, and tuberculosis. The USA, UK, and EU have been major donors, but wealthy countries with endemic NTDs need to contribute more. Addressing the health effects of NTDs, and the inequities at their root, will require resilient and innovative disease programs, strengthened universal health coverage, and a framework that puts the broader determinants of NTDs at its center.

NTDs are, in essence, diseases of poverty. Not only do they affect the poorest and most marginalized communities around the world, but they also fuel a vicious cycle of poor health and poverty. The associated loss of income affects not only households but also communities, the health systems they rely on, and ultimately, national economies.

The Kigali Declaration, signed in June 2022, takes this aspect one step further. It specifically calls on the public and private sector to work together to supplement these efforts, highlighting the need for concerted efforts from all stakeholders involved and renewed funding. In other words, governments and donors must make the commitment to eliminate NTDs a high priority.

However, because COVID-19 has severely disrupted access to health care services and programs, strengthening fragile health systems equipped to deal with seemingly competing health threats has been challenging. Addressing this and building resilience will be crucial in ensuring that the pandemic does not result in a resurgence of diseases, putting more people at risk of harm.

“ It turns out that monkeypox emerged out of its Central African endemic zone into West Africa in 2017, five years ago, and the outbreak has been ongoing for five years with no urgency, no response, no World Health Organization (WHO) engagement around vaccines in those countries.”

—Professor Chris Beyrer
Johns Hopkins University

With Inputs from *Lancet* & WHO

Original Study

Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: A prospective observational cohort study

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SUMMARY

Background In May, 2022, several European countries reported autochthonous cases of monkeypox, which rapidly spread globally. Early reports suggest atypical presentations. We aimed to investigate clinical and virological characteristics of cases of human monkeypox in Spain.

Methods This multicentre, prospective, observational cohort study was done in three sexual health clinics in Madrid and Barcelona, Spain. We enrolled all consecutive patients with laboratory-confirmed monkeypox from May 11 to June 29, 2022. Participants were offered lesion, anal, and oropharynx swabs for PCR testing. Participant data were collected by means of interviews conducted by dermatologists or specialists in sexually transmitted infections and were recorded using a standard case report form. Outcomes assessed in all participants with a confirmed diagnosis were demographics, smallpox vaccination, HIV status, exposure to someone with monkeypox, travel, mass gathering attendance, risk factors for sexually transmitted infections, sexual behaviour, signs and symp-

toms on first presentation, virological results at multiple body sites, co-infection with other sexually transmitted pathogens, and clinical outcomes 14 days after the initial presentation. Clinical outcomes were followed up until July 13, 2022.

Findings 181 patients had a confirmed monkeypox diagnosis and were enrolled in the study. 166 (92%) identified as gay men, bisexual men, or other men who have sex with men (MSM) and 15 (8%) identified as heterosexual men or heterosexual women. Median age was 37·0 years (IQR 31·0–42·0). 32 (18%) patients reported previous smallpox vaccination, 72 (40%) were HIV-positive, eight (11%) had a CD4 cell count less than 500 cells per µL, and 31 (17%) were diagnosed with a concurrent sexually transmitted infection. Median incubation was 7·0 days (IQR 5·0–10·0). All participants presented with skin lesions; 141 (78%) participants had lesions in the anogenital region, and 78 (43%) in the oral and perioral region. 70 (39%) participants had complications requiring treatment: 45 (25%) had a proctitis, 19 (10%) had tonsillitis, 15 (8%) had penile oedema, six (3%) an abscess, and eight (4%) had an exanthem. Three (2%) patients required hospital admission. 178 (99%) of 180 swabs from skin lesions collected tested positive, as did 82 (70%) of 117 throat swabs. Viral load was higher in lesion swabs than in pharyngeal specimens (mean cycle threshold value 23 [SD 4] vs 32 [6], absolute difference 9 [95% CI 8–10]; p<0·0001). 108 (65%) of 166 MSM reported anal-receptive sex. MSM who engaged in anal-receptive sex presented with proctitis (41 [38%] of 108 vs four [7%] of 58, absolute difference 31% [95% CI 19–44]; p<0·0001) and systemic symptoms before the rash (67 [62%] vs 16 [28%], absolute difference 34% [28–62]; p<0·0001) more frequently than MSM who did not engage in anal-receptive sex. 18 (95%) of 19 participants with tonsillitis reported practising oral-receptive sex. The median time from onset of lesions to formation of a dry crust was 10 days (IQR 7–13).

Interpretation In our cohort, monkeypox caused genital, perianal, and oral lesions and complications including proctitis and tonsillitis. Because of the variability of presentations, clinicians should have a low threshold for suspicion of monkeypox. Lesion swabs showed the highest viral loads, which, combined with the history of sexual exposure and the distribution of lesions, suggests close contact is probably the dominant transmission route in the current outbreak.

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INTRODUCTION

Autochthonous cases of monkeypox infection were initially confirmed in England from May 6, 2022,[1] and subsequently throughout Europe.[2] In Spain, as in other countries, the current outbreak has mainly affected men who have sex with men (MSM) without any documented history of travel to countries where monkeypox is endemic. By June 27, more than 800 cases had been reported in Spain.[3] The pathogen has been identified as monk-

eypox virus from the West African clade, which is often associated with milder disease than the Congo basin clade. Nevertheless, some outbreak clade mutations have been identified in proteins involved in virus transmission and virulence.[1]

Infections caused by orthopoxviruses can be classified as either systemic or localised (at the site of virus entry).[4] The type of infection depends on the species of orthopoxvirus, the route of entry, and the species and genus of susceptible animals and their immune status. Typically, generalised infections caused by orthopoxviruses manifest as a diffuse rash. By contrast, clinical descriptions of smallpox cases from early medical writings describe a localised rash at the site of virus entry following cutaneous inoculation.[5,6]

Historically, the signs and symptoms of monkeypox in countries in Africa where it is endemic consisted of a characteristic rash of several hundred simultaneous lesions in multiple regions of the body, including the face, arms, legs, and less commonly the palms, soles, or genitalia.[7–13] The rash was normally preceded by prodromal symptoms such as fever, lymphadenopathy, and influenza-like symptoms. Initial evidence from the current outbreak suggests cases are atypical, with the rash in fewer regions of the body, in particular the genital and perianal areas, without spread to other body regions and with a relative mildness or absence of prodromal symptoms.[14]

Detailed information regarding the epidemiology and the clinical features of monkeypox in the 2022 outbreak is scarce. In this study, we aimed to comprehensively evaluate the epidemiology, clinical features, and virological features of patients diagnosed with monkeypox at three large hospitals in Spain.

METHODS

Study design and participants

In this multicentre, prospective, observational cohort study we enrolled all consecutive patients diagnosed with monkeypox from May 11 to June 29, 2022, at three hospitals in Spain (Hospital Universitario 12 de Octubre, Madrid; BCN Checkpoint Sexual Health Clinic, University Hospital Germans Trias i Pujol, Barcelona; and Drassanes Sexual Health Clinic, University Hospital Vall d'Hebron, Barcelona). The first is a public general hospital, and the last two are open-access, community-based sexual health clinics. Together, the three units treat approximately 100 patients with sexually transmitted infections each day. All participants suspected to have monkeypox were offered triple-site (ie, lesion, anal, and oropharynx swabs) monkeypox PCR testing. A confirmed case of monkeypox was defined as a positive result on high throughput sequencing or real-time RT-PCR assay of skin lesion, anal, or oropharynx swab specimens. Only patients with laboratory-confirmed monkeypox were included in the analysis.

The study was approved by the Ethics Committee of the Hospital Germans Trias i Pujol. Oral informed consent was obtained from all participants. Written informed consent for anonymised publication of images was individually sought and obtained from participants.

PROCEDURES

Twelve dermatologists or specialists in sexually transmitted infections interviewed participants for this study. We obtained demographic, epidemiological, clinical presentation, laboratory, and clinical outcome data using a standardised case report form. Data on sexual history, including sexual practices, and the number of sexual partners were also collected. Clinical outcomes were followed up to July 13, 2022. The case definitions were established before the start of data collection. Broadly, case definitions consisted of participants with one or more papular, vesicular, or pustular skin lesion, or signs or symptoms of proctitis. When a new sign or syndrome was identified, the case definition was agreed upon by all recruiting physicians. If any data were missing or clarification was needed, we obtained the information by direct communication with the patient.

Laboratory confirmation of monkeypox was done at the Spanish National Microbiology Centre reference laboratory before June 6, 2022, and subsequently in local certified tertiary care hospitals. Skin lesion, anal, and oropharynx swabs were collected and examined with real-time RT-PCR. Monkeypox virus DNA was detected by LightMix Modular Orthopox Virus assay (TIB MolBiol, Berlin, Germany) on LightCycler 480 Real-Time PCR equipment (Roche Applied Science, Mannheim, Germany) amplifying a 113-base-pair long fragment of the 14 kDa gene specific to orthopoxviruses. A comprehensive sexual health screen was offered to all individuals, including a fourth-generation enzyme immunoassay for HIV serology, syphilis serology (Alinity i Syphilis TP [Abbott, Chicago, IL, USA] and Axis-Shield RPR [Abbott]), and triple-site *Chlamydia trachomatis, Neisseria gonorrhoeae, and Mycoplasma genitalium* screening from a pharyngeal swab, a rectal swab, and a first-void urine sample (Allplex STI Essential Assay [Seegene, Seoul, South Korea] or Aptima Combo 2 assay [for *C trachomatis and N gonorrhoeae;* Hologic, Marlborough, MA, USA] and Aptima *M genitalium* assay [Hologic]). Additionally, participants presenting with clinical signs of proctitis

Table 1. Demographic and epidemiological characteristics of participants

		Participants (n=181)
Age, years		37·0 (31·0–42·0)
Sex		
	Female	6 (3%)
	Male	175 (97%)
Ethnicity		
	Spanish	79 (44%)
	South and central American	82 (45%)
	Other	19 (10%)
	Missing data	1 (1%)
Sexual orientation		
	Gay men, bisexual men, and other men who have sex with men	166 (92%)
	Heterosexual men	9 (5%)
	Heterosexual women	6 (3%)
History of smallpox vaccination		32 (18%)
HIV-positive		72 (40%)
Possible exposure to monkeypox		
	Regular sexual partner with monkeypox	47 (26%)
	Household contact with monkeypox	6 (3%)
	Attendance at a Pride event	66 (36%)
	Recent travel out of Spain	26 (14%)
Sexual risk factors		
	Number of sexual partners in past 14 days	2·0 (1·0–5·0)
	Number of sexual partners in past 3 months	6·5 (3·0–16·0)
	Sexually transmitted infection in past 12 months	99 (55%)
	Use of social media apps to identify sexual partners	107 (59%)
	Sex outside of Spain in past 3 months	15 (8%)
	Sex with a sex worker	8 (4%)
	Use of recreational drugs during sex	57 (31%)
Type of sexual practice		
	Vaginal-insertive sex	11 (6%)
	Vaginal-receptive sex	6 (100%)*
	Anal-insertive sex	131 (72%)
	Anal-receptive sex	108 (60%)
	Oral-insertive sex	160 (88%)
	Oral-receptive sex	158 (87%)

Data are median (IQR) or n (%).
* Six (100%) of six female participants.

were screened for *Treponema pallidum* DNA using PCR in rectal swabs (Allplex STI Genital Ulcer assay; Seegene]) and participants with tonsillitis were screened for group A *Streptococcus* (Abbott SD Bioline rapid antigen detection test [Abbott]). All procedures were done as planned, with no deviations from the approved study protocol.

OUTCOMES

In all participants, we described demographics, patient-reported historic smallpox vaccination, comorbidities (including HIV status), epidemiological data (ie, incubation period, exposure to someone with monkeypox, travel, mass gathering attendance, and risk factors for sexually transmitted infections), sexual practices, signs and symptoms on first presentation, virological results at multiple body sites (including analysis of cycle threshold values), co-infection with other sexually transmitted pathogens, and clinical outcomes 14 days after the initial presentation to determine progression of disease.

We classified sexual orientation as heterosexual or MSM, including gay and bisexual men. For the purpose of analysis, we differentiated three presumed routes of infection that might be relevant for pathogenesis: anal-receptive sex in MSM, non-anal-receptive sex in MSM, and non-MSM sex. The first and second categories were mutually exclusive, so participants who had receptive anal intercourse were classified in the first group regardless of whether they had engaged in other types of sexual activity. The incubation period was defined as the interval between the potential earliest date of contact with a presumed transmission source (ie, a person with suspected or confirmed monkeypox) and the potential earliest date of symptom onset (ie, influenza-like symptoms or skin rash). To calculate the incubation period, we excluded participants whose timing of exposure was unclear. We defined at least one systemic feature as the presence of any influenza-like illness, fever, headache, or arthralgia. Skin rash severity was classified as moderate when there were more than 20 lesions, mild when there were three to 20 lesions, and minimal when there were one or two lesions.[5] Acute proctitis was defined as rectal pain and tenesmus or purulent discharge, tonsillitis as sore throat or trouble swallowing and acute enlargement and reddening of the tonsil or tonsils, moderate to severe penile oedema as swelling of the penile glans or foreskin, such that the retracted foreskin cannot be returned to its anatomic position (ie, paraphimosis), and exanthem as a widespread rash of pink-to-red spots on the trunk, arms, and legs.

Table 2. Clinical characteristics on first presentation and laboratory results

		Participants (n=181)
Incubation period, days*		7·0 (5·0–10·0)
Systemic features		
	At least one systemic feature	160 (88%)
	Systemic symptoms before the rash onset	87 (48%)
	Influenza-like illness	147 (81%)
	Fever	131 (72%)
	Headache	96 (53%)
	Sore throat	66 (36%)
Clinical features of the rash		
	Approximate number of lesions	
	>20	15 (8%)
	3–20	145 (80%)
	1–2	21 (12%)
	Number of body regions involved	3 (2–4)
	Lesion morphology	
	Papular lesions	38 (21%)
	Vesicular lesions	47 (26%)
	Pustular lesions	162 (90%)
Lesion location		
	Genital	100 (55%)
	Perianal	66 (36%)
	Oral ulcer	45 (25%)
	Perioral	51 (28%)
	Hands and feet	108 (60%)
	Trunk and extremities	104 (57%)
Lymphadenopathies		
	Any lymphadenopathy	153 (85%)
	Lymphadenopathy by region	
	Cervical	53 (29%)
	Inguinal	110 (61%)
	Axillary	2 (1%)
	None	28 (15%)

		Participants (n=181)
Complications		
	Proctitis	45 (25%)
	Tonsillitis	19 (10%)
	Penile oedema	15 (8%)
	Bacterial skin abscess	6 (3%)
	Exanthem	8 (4%)
Investigations		
	PCR of skin swab positive†	178/180 (99%)
	Mean cycle threshold value of positive skin specimens	23 (4)
	PCR of throat swab positive†	82/117 (70%)
	Mean cycle threshold value of positive throat specimens	32 (6)
	PCR of anal swab positive†	43/55 (78%)
	Mean cycle threshold value of positive anal specimens	27 (7)
Concurrent sexually transmitted infection		
	Any sexually transmitted infection	31 (17%)
	HIV	1 (1%)
	Chlamydia	10 (6%)
	Gonorrhoea	6 (3%)
	Herpes simplex virus	2 (1%)
	Mycoplasma genitalium	2 (1%)
	Syphilis	13 (7%)
Outcomes		
	Time to formation of dry crust, days	10·0 (7·0–12·5)
Admitted to hospital		
	No	178 (98%)
	Clinical management	2 (1%)
	Social reasons	1 (1%)

Data are median (IQR), n (%), n/N (%), or mean (SD).
* n=144; 37 participants had missing data.
† Denominators are smaller than the total number of participants because some participants did not have these PCR tests done.

STATISTICAL ANALYSIS

Continuous variables were expressed as medians and IQRs or ranges, as appropriate. Categorical variables were summarised as absolute values and proportions. No imputation was made for missing data. We described clinical features, including the distribution of skin lesions and the incubation period stratified by the presumed route of exposure, and PCR cycle threshold values by pharyngeal or ulcer swab. Analyses were considered descriptive and exploratory. We compared continuous variables using the *t* test and proportions using a χ^2 test. All tests were two-sided with a significance threshold of 0·05. All analyses were performed with R (version 3.6.2).

RESULTS

181 patients with monkeypox were assessed at the three participating centres during the study period, all of whom consented to take part in the study (99 at Hospital Universitario 12 de Octubre, 67 at BCN Checkpoint, and 15 at Drassanes). The demographic and clinical characteristics of the participants are shown in

table 1. 175 (97%) of 181 participants were male and six (3%) were female. The median age of the participants was 37·0 years (IQR 31·0–42·0, range 19·0–58·0). 72 (40%) participants were HIV-positive, 71 (99%) of whom were on antiretroviral therapy, and eight (11%) had a CD4 cell count of less than 500 cells per µL. No individuals were identified without any potential sexual exposures (table 1) and travel to endemic regions was not reported by any participant.

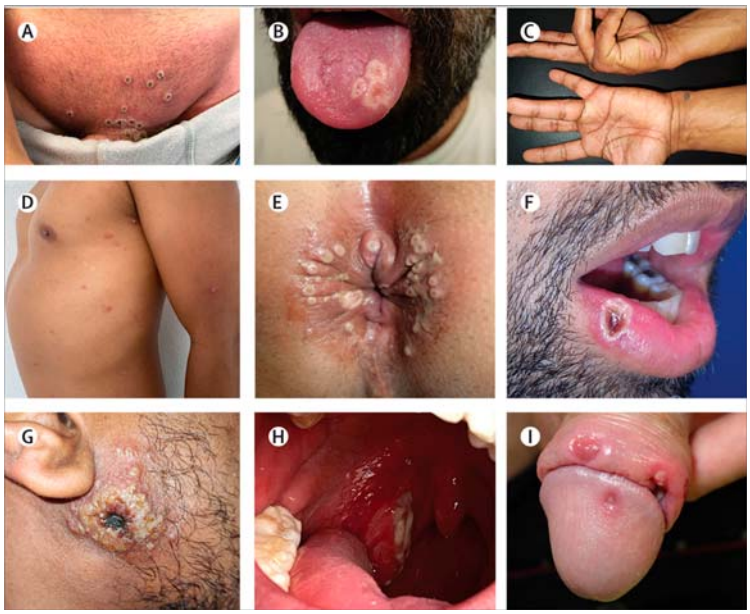
The median incubation period was 7·0 days (IQR 5·0–10·0, range 1·0–19·0). The numbers of participants with systemic features are shown in table 2. All participants presented with skin lesions; 141 (78%) participants had lesions in the anogenital region, and 78 (43%) had lesions in the oral and perioral region (table 2; figure 1). The number of skin lesions was 20 or fewer in 166 (92%) participants. No patients presented with generalised swelling of the lymph nodes as part of the systemic illness, but localised lymphadenopathy in relation to lesion location was observed in 153 (85%) participants. Complications that required medical treatment were described in 70 (39%) participants, most frequently pain relief for proctitis, tonsillitis, and in participants with anal lesions. 41 (91%) of 45 participants with proctitis reported practising receptive anal sex and five (11%) had concurrent chlamydia or gonorrhoea diagnosed from a rectal swab. Of the 19 participants with tonsillitis, all had white ulcerative lesions on the tonsils and a negative group A Streptococcus antigen test, and 18 (95%) reported practising oral-receptive sex. Bacterial abscess with culture confirmation were most often around the perianal area and the face (appendix p 9). 15 (8%) participants presented with preputial oedema or gross oedema of the penile glans resulting in paraphimosis. Eight (4%) participants developed a widespread maculopapular exanthem (table 2), five (3%) were diagnosed with a morbilliform drug eruption related to B-lactams, one (1%) had a viral exanthem, one (1%) had an urticarial exanthem, and one (1%) had an erythema multiforme. We did not identify an alternative infectious cause in these patients. We did not notice any difference in clinical features, including the number of lesions, or incubation period between patients who reported being HIV-positive and those who did not, or between patients who reported receiving smallpox vaccination and those who did not (appendix pp 5–8).

Triple-site swabbing was offered to the 114 participants at two of the three sexual health clinics, but the 67 participants at BCN Checkpoint were offered only lesion swab collection. The proportions of skin, throat and anal swabs that were positive are shown in table 2. The mean cycle threshold value of positive lesion swabs was significantly lower (ie, higher viral load) than from positive pharyngeal swabs (23 [SD 4] *vs* 32 [6], absolute difference 9 [95% CI 8–10]; p<0·0001) (figure 2A) and this was true regardless of where the skin lesions were found (data not shown). The mean cycle threshold value of anal swabs was 27 (SD 7). When we excluded participants with oral lesions or tonsillitis that could cause contamination of throat swabs, 38 (63%) of 60 oropharyngeal specimens were positive, with a mean cycle threshold value of 34 (SD 4). Similarly, when we excluded participants with anal lesions or proctitis, 14 (58%) of 24 anal swabs were positive, with a mean cycle threshold value of 30 (SD 7). Neither time from onset of symptoms nor HIV status was associated with different cycle threshold values for samples (appendix p 4). Sequencing of 23 genomes with 100% coverage of specimens collected in Spain indicates that these genomes belong to the west African clade[15,16] and are almost identical to other genomes uploaded from other European countries. A concurrent sexually transmitted infection on this presentation was diagnosed in 31 (17%) of 181 participants, most commonly chlamydia (n=10) and syphilis (n=13).

MSM who engaged in anal-receptive sex presented with proctitis more frequently than MSM who did not engage in anal-receptive sex (41 [38%] of 108 vs four [7%] of 58, absolute difference 31% [95% CI 19 to 44]; p<0·0001; figure 2B, table 3). MSM who engaged in anal-receptive sex also presented with systemic symptoms before the rash more frequently than MSM who did not engage in anal-receptive sex (67 [62%] vs 16 [28%], absolute difference 34% [28 to 62]; p<0·0001); there was no difference in incubation times between the two groups (median 8·0 days [IQR 5·0–10·0] vs 7·0 days [5·0–9·0], absolute difference 1 day [–1·4 to 1·2]; p=0·88; table 3, figure 2C). Among participants with throat PCR available, MSM reporting anal-receptive sex had a higher positivity rate in throat specimens (49 [82%] of 60 vs 24 [57%] of 42; p=0·013), presumably reflecting a higher rate of distant dissemination.

Six participants received treatment with topical cidofovir. None received tecovirimat. The median time from the onset of lesions to the formation of a dry crust was 10 days (IQR 7–13, range 2–24) and was broadly similar between people who were HIV-positive (median 11 days [IQR 8–14 days]) and people who were not HIV-positive (median 10 days [7–12]; appendix p 5). The majority of participants were managed as outpatients, with only three (2%) requiring admission to hospital: two (67%) for

Figure 1. Clinical presentation of monkeypox



(A) Pustules in the genital and pubic region, in which the initial umbilication has progressed to necrotic crust with central depression. (B) Three semiconfluent pustular lesions with a depressed centre located on the left side of the tongue dorsum. (C) Pearly acral vesicles embedded in the thick stratum corneum of the palmar skin, shotty on palpation. (D) Scattered papules, pustules, and umbilicated pustules surrounded by an erythematous halo on the lateral aspect of the chest and left arm. (E) Pustules circumferentially distributed on the anal margin and perianal skin. (F) A pustular lesion with a crusted centre on the semimucosa of the lower lip, close to the right oral commissure. (G) Primary inoculation site with a large, crusted lesion on the right cheek. (H) The right palatine tonsil is reddened and enlarged and has a fibrin-covered ulcer. (I) The penile glans and foreskin have lesions of varying sizes and stages of evolution, with oedema surrounding the larger ulcer. Pictures A–C, E–G, and I were taken by EJT-V; pictures D and H were taken by MU.

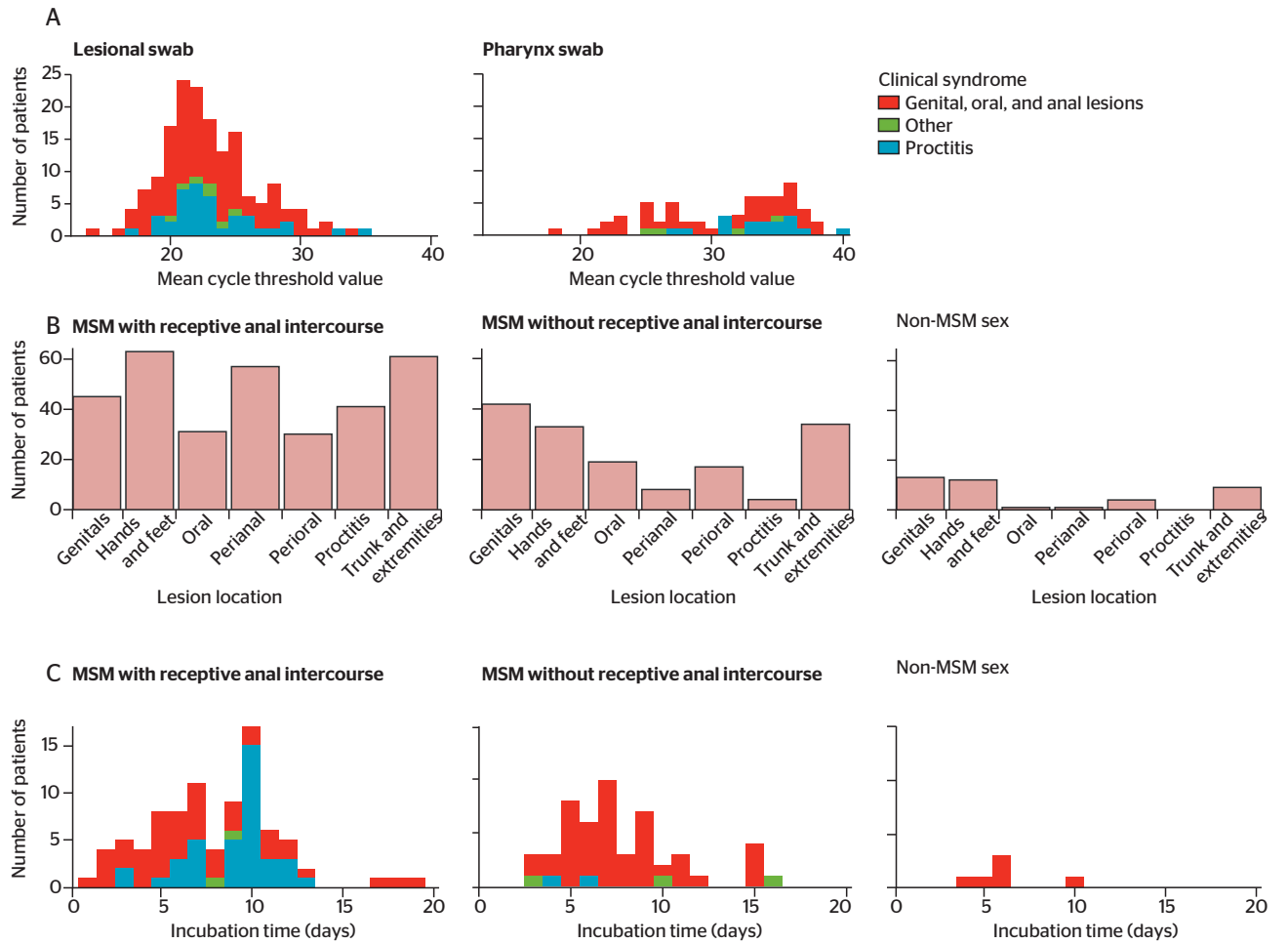
management of bacterial abscesses and one (33%) for social reasons. There were no deaths.

DISCUSSION

In the early stages of the monkeypox outbreak in 2022, diagnosis and disease control have been difficult because many cases have not followed the patterns of illness described in the medical literature. In concert with recent studies,[1,17–19] we found that most participants presented with a low number of lesions located in one or more of the genitals, oral, and anal regions and that systemic symptoms were very common. Almost half of the participants had systemic illness before the rash appeared (prodromal stage) and just over half had systemic illness shortly afterwards (early clinical stage). These symptoms are attributable to the invasive phase of illness, which might sometimes occur after lesions have formed at the site of inoculation. During the invasive phase, the virus might spread to distant areas such as the face, limbs, and trunk and cause lesions at a different stage of progression than the initial local rash. In contrast to previous reports of monkeypox virus infections, no generalised swelling of the lymph nodes was observed, but regional lymphadenopathies were often present in the lymph catchment area of lesions. Nearly all participants had previous sexual exposure to an individual known to have monkeypox or had risk factors for sexually transmitted diseases, such as multiple sexual partners in the 12 weeks before their monkeypox diagnosis or use of recreational drugs during sex. The fact that 32 individuals acquired monkeypox despite smallpox vaccination in their childhood is of note and warrants further investigation to better understand the protection provided by vaccination in the context of the current outbreak. Additionally, 40% of individuals were HIV-positive, including eight participants with a CD4 cell count of less than 500 cells per µL. Neither the severity nor the progression of the disease differed between people who were HIV-positive and the rest of the participants. Given the high CD4 counts of participants in this study, we cannot comment on whether more immunosuppressed individuals might develop more severe disease. Due to the sampling strategy, we could not assess whether people who were HIV-positive were more susceptible to monkeypox infection because half of the participants were recruited from a hospital that provides health services to many individuals with HIV.

More than a third of participants presented with complications that required pain-relief medication. The most common complications were proctitis (sometimes extremely painful and in other cases associated with very intense itching), tonsillitis, paraphimosis due to penile oedema, and bacterial abscesses. Participants reporting anal-receptive sex were more likely than others to have early systemic symptoms before developing skin lesions. One explanation is that anal sex might damage the epithelium and enable blood entry, allowing greater

Figure 2. Mean cycle threshold values by swab location and location of skin lesions and incubation periods by presumed route of infection



(A) Mean cycle threshold values as a proxy for viral load for lesional swabs compared with pharynx swabs. (B) Location of skin lesions by presumed route of infection. (C) Incubation period of monkeypox by presumed route of infection and location of lesions. MSM=men who have sex with men.

viraemia at an early stage when local lesions have not yet developed. An alternative explanation is that these participants did have rectal lesions at the time of initial presentation, but these were missed. A similar phenomenon has been observed in patients with syphilis: MSM are less likely to present with primary syphilis because rectal chancres are often missed.

There are questions about whether monkeypox is sexually transmitted via semen and vaginal secretions. However, the extended definition of sexually transmitted infections such as syphilis and herpes simplex includes the presence of pathogens in purulent genital lesions that are transmitted through superficial abrasions in the skin or mucous membranes.[20] Anorectal and genital epithelium routes exhibit the highest probability of sexually transmitted infection acquisition because they have a lower degree of keratinisation and a higher frequency of antigen-presenting cells such as macrophages and dendritic cells.[21] Using the PCR cycle threshold as a proxy, we found that viral load in lesions was significantly higher than in pharyngeal swabs. Although imprecise, these findings are consistent with a viral load more than three orders of magnitude higher in lesion samples compared with respiratory samples. This observation, together with the localisation of the lesions, the exposure history of the individuals, and the concurrent sexually transmitted infections, suggests that close contact during sex is the dominant form of monkeypox transmission in the current outbreak. Public health messaging needs to be targeted at appropriate populations who might be at risk and needs to be adapted to highlight the risk of transmission related to close skin-to-skin contact.

Table 3. Association between the presumed route of transmission and epidemiological, clinical, and virological factors

		MSM with receptive anal contact (n=108)	MSM without receptive anal contact (n=58)	Non-MSM sex (n=15)	Total (n=181)
Incubation period, days		8·0 (5·0–10·0)	7·0 (5·0–9·0)	6·0 (5·0–6·0)	7·0 (5·0–10·0)
Systemic symptoms before the rash		67 (62%)	16 (28%)	4 (27%)	87 (48%)
Presence of proctitis		41 (38%)	4 (7%)	0	45 (25%)
Throat PCR					
	Not done	48 (44%)	16 (28%)	0	64 (35%)
	Negative	11 (11%)	18 (31%)	6 (40%)	35 (19%)
	Positive	49 (45%)	24 (41%)	9 (60%)	82 (45%)

Data are median (IQR) or n (%). MSM=men who have sex with men.

Our finding of low viral loads or even negative results in respiratory samples suggests that there might be differences from previous imported cases, which have shown prolonged monkeypox virus DNA detection in swabs of the upper respiratory tract.[11] We speculate that local replication of the virus at the point of entry within lesions of the genital or oral tract might be followed by low-grade or no viraemia, resulting in minimal replication in the respiratory tract and little or no transmission through respiratory droplets. In smallpox, accidental local inoculation or intentional inoculation (ie, variolation) resulted in locally restricted satellite lesions around the point of entry in the absence of disseminated lesions.[5,6] By contrast, generalised poxvirus infections progress in a stepwise manner (with an initial amplification of viral load in the lymph nodes, liver, and spleen), resulting in a high-grade viraemia that leads to disseminated infection of the skin and respiratory tract, and the excretion of infective respiratory droplets.[22–25] Besides the change in the route of transmission, there might be alternative reasons for the localised presentation of monkeypox, such as a novel gain-of-function mutation, that might become evident when more viral sequences are available. Additionally, mild trauma in the pubic, inguinal, and perianal regions during sexual intercourse might cause local vasodilation and a higher density of skin lesions in that particular region (also known as the garter effect).[6]

Our study has some limitations. First, we could not estimate the incubation period in 37 participants because they reported multiple possible exposure events. Second, participants from one of the sexual health clinics did not undergo collection of a throat or anal swab on presentation due to logistical reasons. Third, we only collected samples at diagnosis and did not collect semen samples as part of this study. We are collecting samples, including semen, at multiple timepoints in a currently enrolling study, which might provide more information on viral kinetics (NCT05476744). Similarly, we did not have complete information on skin healing (eg, desquamation of crust and new skin underneath) and had to use the formation of dry crust as the parameter for assessing lesion healing. Finally, blood testing was not routinely done; therefore, we had to infer dissemination from the point of entry to a distant site on the basis of testing of throat swabs, which might have underestimated the number of participants with viraemia. Nevertheless, many participants had samples collected at more than one body site, which enabled us to investigate associations between rash distribution and dissemination of the virus.

Our study strengthens the evidence for skin-to-skin contact during sex as the dominant mechanism of transmission of monkeypox, with important implications for disease control. First, the putative change compared with previous outbreaks in the route of transmission from respiratory to direct contact might promote the spread of the disease through sexual networks. This scenario is similar to previous outbreaks, such as lymphogranuloma venereum L2b, antibiotic-resistant *Shigella*, and hepatitis A, which were transmitted predominantly within sexual networks of MSM.[26] Second, because monkeypox might present with atypical manifestations, clinicians should have a high index of suspicion of the disease, particularly in individuals living in areas with high transmission rates or with potential exposure. Specifically, we describe a proctitis-related clinical syndrome, with different clinical features, including systemic manifestations before lesion onset, in individuals reporting anal-receptive sex, which differs from other presentations. Third, because of the short incubation period, pre-exposure vaccination of groups who are at high risk is likely to be more effective than postexposure vaccination for public health control of the infection. Finally, the strikingly higher viral loads in lesion swabs than in pharyngeal swabs should be further

investigated to guide the decision on whether respiratory transmission is relevant and respiratory isolation at home is necessary.

Contributors

EJT-V, CG-Ca, MM, PLO-R, and OM conceived and designed the study. All authors acquired the data. EJT-V, MM, and OM analysed and interpreted the data. EJT-V, MM, and OM did the statistical analysis. EJT-V, AAl, CS, MA-D, MU, CG-Ca, MM, and OM drafted the manuscript. All authors reviewed the manuscript and vouch for the accuracy and completeness of the data and for the adherence of the study to the protocol. All authors were responsible for the final decision to submit for publication. All authors have seen and approved the manuscript. EJT-V, AAl, MU, MM, and OM had full access to all of the data in the study.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified participant data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available from the corresponding author on reasonable request.

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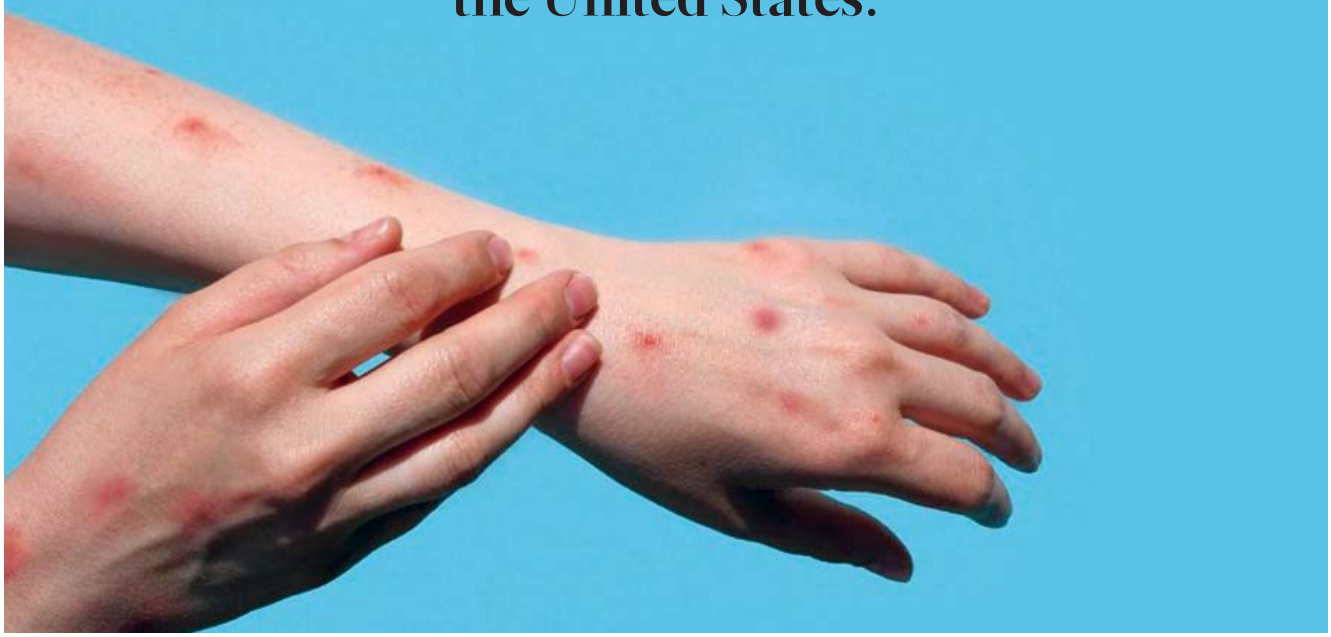
Monkeypox

By **Adam Sherwat, M.D., John T. Brooks, M.D., Debra Birnkrant, M.D., and Peter Kim, M.D.**

Tecovirimat and the Treatment of Monkeypox — Past, Present, and Future Considerations

Now, 34 years later, we are faced with an uncannily similar situation. An unprecedented outbreak of monkeypox has emerged, which at present is disproportionately affecting men who have sex with men in numerous countries where the disease is not endemic, including the United States.



In 1988, the human immunodeficiency virus (HIV) was rapidly spreading worldwide and disproportionately devastating certain communities, most notably gay, bisexual, and other men who have sex with men.

Even after promising new pharmacologic therapies were finally developed, the existing processes for approving their use in humans were painfully slow. Spurred by the AIDS Coalition to Unleash Power (ACT UP) and other advocacy groups, federal scientists and policymakers worked with affected persons to find a way forward that balanced two ethical imperatives: honoring the right of people with serious illness to access potentially beneficial treatment and upholding the responsibility of the health care and public health communities to ensure that those treatments were safe and effective. The result was improvements to the regulatory process designed to accelerate access to and expedite approvals for drugs that treat a serious disease.

Now, 34 years later, we are faced with an uncannily similar situation. An unprecedented outbreak of monkeypox has emerged, which at present is disproportionately affecting men who have sex with men in numerous countries where the disease is not endemic, including the United States. Although not as life-threatening as HIV, monkeypox can cause serious illness, including ocular involvement, soft-tissue superinfections, and excruciating anogenital lesions.[1] In the current situation, there is a drug — tecovirimat, available for clinical use under an expanded-access protocol (https://www.cdc.gov/poxvirus/monkeypox/clinicians/obtaining-tecovirimat.html. opens in new tab) — that might conceivably speed resolution of monkeypox illness and improve outcomes yet poses the same conundrum: how to manage compassionate access to a drug whose safety and efficacy in humans have not been established. Since smallpox and monkeypox are caused by the same genus of viruses, to better understand the role that tecovirimat might play in our response to the monkeypox outbreak, it is important to understand the basis for its approval by the U.S. Food and Drug Administration (FDA) for the treatment of smallpox and the knowledge gaps that remain.

Tecovirimat is an antiviral drug that was approved for the treatment of smallpox disease under a regulation known as the "Animal Rule."[2] This pathway allows for approval of drugs for serious or life-threatening conditions when it is not ethical to conduct efficacy studies in humans and not feasible to conduct field trials to study the effectiveness of a drug or biologic product. Under the Animal Rule, efficacy is established on the basis of adequate and well-controlled studies in animal models of the human disease or condition of interest; safety must be adequately evaluated in people.

Since smallpox is an eradicated disease and conducting efficacy studies in humans would be neither ethical nor feasible, the Animal Rule was the only regulatory pathway for approving a product for the treatment of smallpox. Smallpox is a severe and highly lethal human illness caused by variola virus, a member of the orthopoxvirus genus of viruses. Animal studies using variola virus, including nonhuman primate models, are not consistently reproducible and require unnaturally high viral challenge doses; moreover, variola virus infection in animals does not mimic human smallpox disease. In addition, studies of variola virus present substantial feasibility challenges because research involving the virus is restricted to two maximum-containment laboratories located in the United States and Russia.

Therefore, tecovirimat's efficacy for the treatment of smallpox was established, and the drug approved, on the basis of studies in animal models using related orthopoxviruses — specifically, nonhuman primates infected with monkeypox virus and rabbits infected with rabbitpox virus. In these studies, survival rates were markedly higher among animals that received tecovirimat than among those that received placebo. Safety in humans was evaluated by assessing adverse reactions in healthy volunteers who received tecovirimat. The recommended dose of tecovirimat for the treatment of smallpox in humans was established by comparing plasma concentrations of the drug in healthy volunteers with those in animal models at doses that had been shown to have full effectiveness against monkeypox and rabbitpox. The recommended duration of therapy in humans was also based on findings from studies in animals and in healthy people.

In contrast to smallpox, monkeypox disease remains endemic in some parts of the world (primarily West and Central Africa), and researchers can design clinical

trials that would be both ethical and feasible. Although there are case reports of using tecovirimat to treat patients with monkeypox and other non-variola orthopoxvirus infections, these data are insufficient to demonstrate efficacy. Animal studies may be compelling,[3] but efficacy observed in animals does not always translate directly into efficacy observed in humans in subsequent clinical trials.[4] Safety data for tecovirimat could be obtained from persons with monkeypox illness rather than just healthy volunteers. Thus, studies in humans with monkeypox are both needed and possible.

To that end, and before the onset of the current outbreak, the National Institutes of Health (NIH) had initiated planning for a randomized, controlled trial (RCT) in the Democratic Republic of Congo (DRC) to evaluate the safety and efficacy of tecovirimat in treating monkeypox. However, the current worldwide outbreak involves a different clade of monkeypox virus than that which generally causes monkeypox infection in the DRC, and some of the clinical manifestations of the current outbreak (substantial anogenital and oral mucosal involvement with resultant severe pain) and affected populations at this time (men who have sex with men) differ from those in countries where monkeypox is endemic.[1] Therefore, the NIH is now also developing a U.S.-based RCT to assess the safety and efficacy of tecovirimat for the treatment of monkeypox disease. This trial will be conducted by the AIDS Clinical Trials Group, the research network that was established in the late 1980s to rapidly assess the safety and efficacy of antiretroviral drugs for HIV infection. We anticipate that these trials will provide data needed for clinical and regulatory decision making in the United States.

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We recognize that monkeypox can cause severe disease and that tecovirimat has been shown to have efficacy in animal models of monkeypox and an acceptable safety profile in healthy people. Therefore, while RCTs are under development, the Centers for Disease Control and Prevention (CDC) and the FDA have worked together to streamline the expanded-access process by reducing paperwork and data collection,[5] and we will continue to fine-tune these mechanisms with input from health care providers using this process. In parallel, we believe that it remains critical to conduct RCTs in the United States to determine whether tecovirimat is a safe and effective treatment for monkeypox disease, especially given the disease's clinical presentation in the current outbreak. As was the case with antiretrovirals for HIV in the 1980s, without data from RCTs, we will not know whether tecovirimat would benefit, harm, or have no effect on people with monkeypox disease. The CDC, the FDA, and the NIH will continue to work together to provide access to tecovirimat for compassionate use while appropriately evaluating its safety and efficacy in RCTs.

From the Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring (A.S., D.B.), and the National Institute of Allergy and Infectious Diseases, Bethesda (P.K.) — both in Maryland; and the Multinational Monkeypox Outbreak Response, Centers for Disease Control and Prevention, Atlanta (J.T.B.).

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Biomarkers

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Exosomal Biomarkers for Neurologic Conditions: A New Frontier

We discuss pros and cons of existing blood biomarkers, as well as introduce a new methodology that may revolutionize the biomarker field.

Introduction

A great challenge regarding diagnosis of neurologic diseases today is the lack of stable and validated biomarkers that can reliably detect disease pathology early enough to provide a window for preventative treatment. Likewise, there are few validated biomarkers that can reliably detect changes in the brain as a result of interventions. Even though blood biomarkers have shown some promise, there are great variabilities between different studies related to experimental conditions and the size of the cohort tested. In the current article, we discuss pros and cons of existing blood biomarkers, as well as introduce a new methodology that may revolutionize the biomarker field.

Biomarkers, including blood, cerebrospinal fluid (CSF), or imaging techniques, have been used to simplify the diagnosis of neurologic diseases during the last couple of decades. They can be classified into several categories, depending on whether they address predictive susceptibility, diagnosis, prognosis, or response to treatment in the clinical course of the disease. The World Federation of Societies of Biological Psychiatry (WFSBP) recently published updated guidelines for pre-analytical handling of samples, biobanking, analysis, and interpretation of the results for fluid biomarkers for dementia.[1]

There are similar considerations for other neurologic diseases, including Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).[2-4] The WFSBP concluded that novel methods for blood analysis, including ultrasensitive biomarker measurements, have revolutionized the field, but large variability still exists between labs. Biomarkers in CSF come with their own difficulties, such as patient reluctance

to undergo a spinal tap, as well as legal implications in some countries and states for performing this relatively invasive procedure on patients who may not be capable of giving their consent. In addition, there are novel imaging techniques, including positron emission tomography (PET) imaging, quantitative magnetic resonance imaging (MRI), and 3D amplified MRI, that can provide better prognostic and diagnostic input regarding patient progression. However, these are not always available at general hospitals and are costly. Therefore, there is a need for more reliable biomarkers obtained via minimally invasive techniques.

Extracellular vesicles are lipid-bound vesicles that are released from every cell in the body and can be divided into three classes based on their size, biogenesis, content, and function: microvesicles, exosomes, and apoptotic bodies (see Figure 1).[5]

Groundbreaking work by the Goetzl group and others has shown that neuron-derived exosomes (NDEs) can be purified from a small blood sample, and NDE cargo (ie, content) can be measured using ultrasensitive assays. The Goetzl group found that amyloid and different forms of phospho-tau are present in NDE cargo decades prior to the onset of dementia symptoms in patients with prodromal Alzheimer's disease.[6] Since then, multiple investigators have verified these findings and strongly suggested the validity of exosomal biomarkers for identifying neurologic diseases.

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Why does this matter?

There are no reliable biomarkers from blood or CSF that can predict onset of neurologic diseases or intervention effects – for example, with a drug intervention. Although recent method development has identified ultrasensitive assays – such as the single molecule array (Simoa), a sensitive digital bead immunoassay platform that is 1,000 times more sensitive than an enzyme-linked immunosorbent assay (ELISA) – the proteins circulating in blood can be diffused by production of similar or the same proteins from peripheral organs and may not accurately depict what occurs in the brain. Likewise, results between different assays may vary significantly if the validity of a specific biomarker has been established from studies in a smaller cohort and then tested in larger groups of patients or in a multisite study.

Contrary to plasma proteins, the exosome carries a specific cargo and specific surface markers ("tags"; see Figure 2) based on the cell of origin. This makes it possible to isolate exosomes originating from neurons, astrocytes, or oligodendrocytes, for example. This is of course very important when it comes to disease diagnostics, as glial versus neuronal exosome cargo varies significantly and may have different implications for treatment of the condition or for diagnostics.

Exosomes are affected by pathologic processes such as neuropathologic aggregation of toxic proteins and have been shown to be a sensitive and early detection tool for neurologic disease, as mentioned above. In turn, exosomes can spread pathology, inflammatory processes, or other messages to receiving cells via membrane fusion, receptor signaling, endocytosis, or endocytic transfer (see Figure 2). This suggests that one could potentially identify early neuronal or glial changes detected in exosome cargo and then treat the disease by modifying either exosome cargo, biogenesis, or release mechanisms. These are novel ideas that have been tested in the cancer field.[7]

What are the implications for extracellular vesicle biomarkers in day-to-day clinical practice?

What are the criteria and challenges that a biomarker must face being considered as a standard diagnostic test in daily clinical practice? First, it is important to know what you will use the specific bio-

marker for. Is it for predictive, diagnostic, or prognostic purposes, or is it to measure response to treatment? Whereas conventional or nonconventional imaging techniques can be used to identify white matter lesions in multiple sclerosis or amyloid (using PET imaging) in Alzheimer's disease, for example, these methods are costly and are not as easily accessible as a common blood sample. Cost and accessibility make it difficult to perform repeated testing in the same patient.

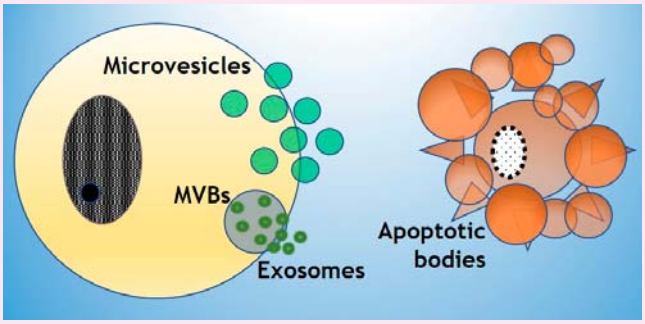
Let's use the example of neurofilament proteins (NfPs) and compare the viability of these proteins as biomarkers for different neurologic diseases. Levels of neurofilament light (NfL) have been shown to be well suited as biomarkers for diverse neurologic conditions because NfL levels are sensitive to neuronal injury across a wide range of neurologic diseases, including Parkinson's disease, multiple sclerosis, and Alzheimer's disease.[8] It has been shown that plasma levels of NfL increase significantly as early as two decades before clinical symptoms occur in familial forms of Alzheimer's disease and one decade before onset of symptoms in sporadic Alzheimer's disease .

A blood-based biomarker must reflect the structural integrity of neurons in the human brain, must be a structural constituent of the neuron, and must also be impacted by neuropathology and easily detectable in blood or other biofluids.[8] NfL fulfills all these criteria but may not be specific for any given neurologic disease and thus not as useful as a diagnostic tool. However, NfL can fill an important void in terms of detecting disease progression after initial diagnosis and documenting intervention effectiveness. In addition, we and others have found that NfL levels in plasma and CSF and in NDEs are highly correlated and therefore have high prognostic value in either fluid measured. This is not the case for other Alzheimer's disease biomarkers, such as p-tau or amyloid.

How will exosomal biomarkers change the future of biomarkers?

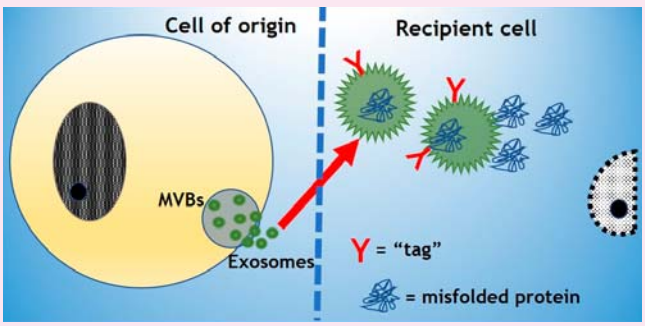
As described above, exosomal biomarkers can represent a more reliable measure of the onslaught of neurologic diseases that afflict the brain. One can consider NDEs as a "liquid biopsy" of the brain, especially when one considers differences in neuron- versus glia-derived exosomal cargo. Exosomal biomarkers may detect what is currently going on in the brain more accurately than plasma biomarkers, for example. An example of this is reported in a recent manuscript by Dutta et al., who found that CNS-derived exosomes purified from blood could distinguish Parkinson's disease from multiple system atrophy (MSA), demonstrating the usefulness of this new method.[9] They showed that the ratio between α-synuclein concentrations in oligodendroglia-derived exosomes versus levels in neuron-derived exosomes was a particularly sensitive biomarker for distinguishing between Parkinson's disease and MSA. Thus, exosomal preparations purified for CNS origin using immunoprecipitation can be a useful new method, for identifying and providing a differential diagnostic tool from a relatively noninvasive blood sample.

Figure 1



Different forms of extracellular vesicles: MVB=multivesicular body. Exosomes (30–100 nm) are formed by literally all cells in the body in MVBs, which then empty their contents to allow exosomes to be released into extracellular space and be either destroyed, transported into body fluids, or taken up by other cells in the vicinity. Apoptotic bodies (50–5,000 nm in diameter) are the result of active cell death (apoptosis) and are not normal components of a healthy cell. Finally, microvesicles (0.1–1.0 µm) are shed from the cell by outward blebbing of the plasma membrane.

Figure 2



Pathology seeding and spread: MVB=multivesicular body. Exosomes contain proteins, noncoding RNA, enzymes, and identifying products that determine the cell of origin ("tags"). During disease, exosomes can also contain misfolded proteins, such as phospho-tau (in TBI and tauopathies), α-synuclein (in synucleinopathies), and/or amyloid (in Alzheimer's disease). Misfolded proteins can act in a prion-like manner and "seed" pathology from one cell to another or between individuals. This seeding and spreading of pathology is made possible by transportation in exosomes, which can then be taken up by other cells. Using exosome-blocking agents originally developed for cancer can potentially stop the spread of pathology from one brain region to another and reduce progression.

Controversies regarding extracellular vesicle biomarkers

There is no doubt that there are obstacles that must be overcome before exosomal CNS biomarkers can be established in clinical practice. For instance, even small changes in detection methods or reagents available on the market can result in significant differences in levels of the same tested biomarker and thereby seriously influence the significance value. The next step is therefore to employ different detection methods to confirm the validity of exosomal biomarkers for use in neurologic prognosis and diagnosis.

Isolation of exosomes can be challenging due to their nonuniform shape (based on the condition of the cell of origin) and variability in concentration, depending on the fluid or tissue from which the sample was isolated. It is also true that there are relatively low amounts of protein in exosomes compared to blood or CSF, for example, rendering it difficult to measure levels reliably with standard assays. This is where the ultrasensitive assays come in.

However, there are demerits for blood biomarkers as well. These include:

- Measurement of proteins in the blood may not reflect what is going on in the brain.
- Proteins are affected by clinical and biologic processes in the blood, which could lead to alterations in levels or metabolic changes in proteins.
- The concentration of specific protein biomarkers may be lower in the blood than in brain tissue.

Because of these shortcomings, CNS-derived exosomal biomarkers could emerge as a viable alternative – measuring what is truly going on in the brain, contrary to plasma.

There are some other controversies associated with this new method. For example, the purification of exosomes from neurons versus glia may not be trivial, as purification assays used may not be entirely specific, and there is a possibility that false positives could be caused by inclusion of other forms of vesicles, such as liposomes, in the preparation. Therefore, one must use rigorous protocols for purification, and there are several methods proposed for diagnostic profiling of exosomal biomarkers, including differential ultracentrifugation or differential ultracentrifugation coupled with OptiPrepTM gradient fractionation.[10]

Conclusions

Despite these challenges in terms of fluid biomarkers, advancement in research has recently resulted in identification of a group of biomarkers (blood or exosome derived) that specifically target early stages of neurologic conditions. This is especially true for NDE biomarkers. However, more research into a panel of validated biomarkers is crucial for predicting and monitoring efficiency of interventions for, as well as early diagnosis and prognosis of, neurologic disease.

Main takeaways

- Exosomes are extracellular vesicles released from almost every cell type in the body.[5]
- They can be purified from all biologic fluids.
- Cargo and release properties are determined by each cell type.[5]
- Purification of neuron-derived or glia-derived exosomes provides a stable source of early detection biomarkers of neurologic disease.[6,10]
- Pathologic compounds are present in exosomal cargo decades before any symptoms may occur.

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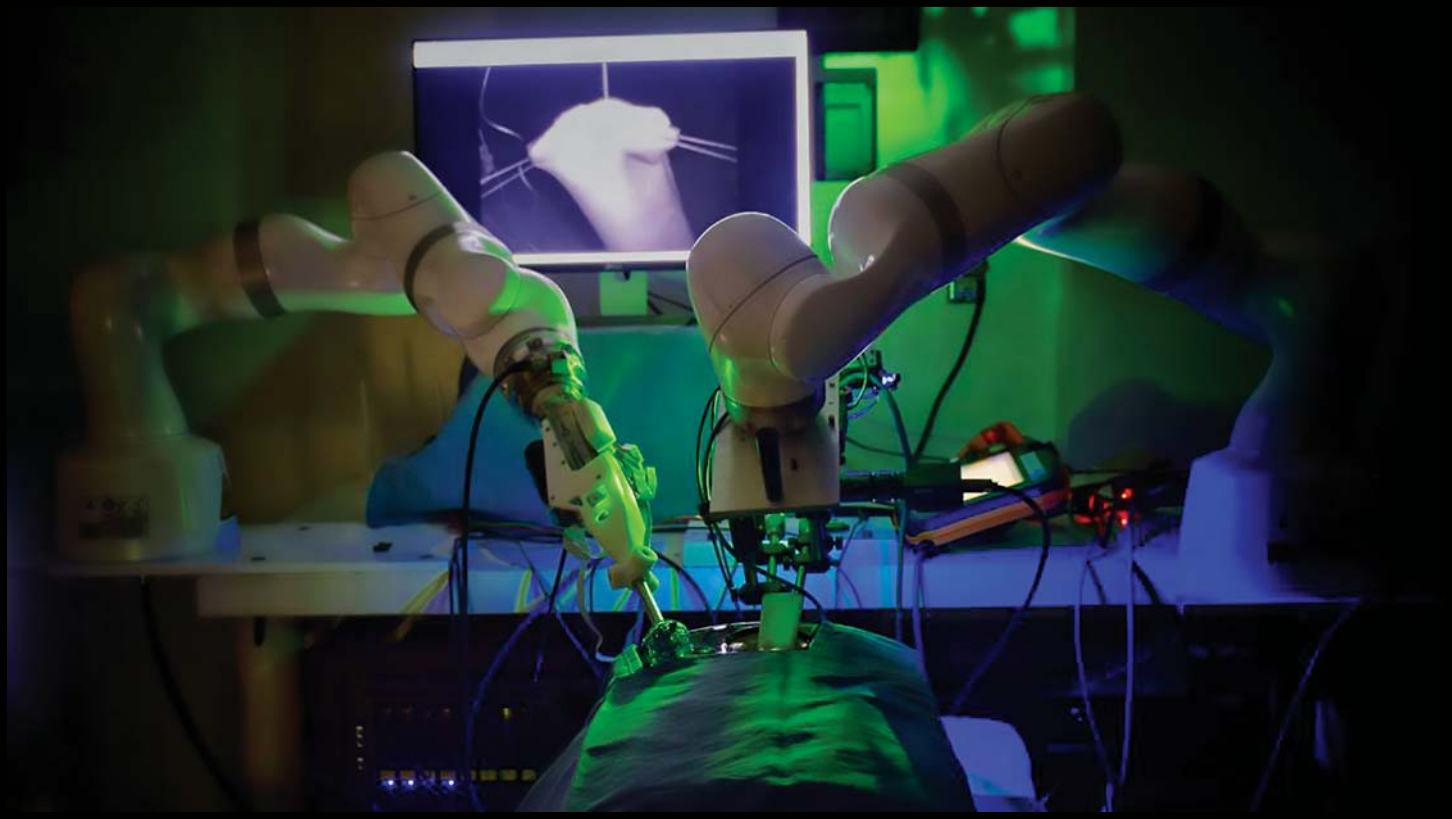
Feature

By **James Gaines**

Handing the Surgeon's Scalpel to a Robot

After decades of merely assisting doctors, are sophisticated machines ready to take charge?



In 2004, the United States' Defense Advanced Research Projects Agency (DARPA) dangled a $1 million prize for any group that could design an autonomous car that could drive itself through 142 miles of rough terrain from Barstow, California, to Primm, Nevada. Thirteen years later, the Department of Defense announced another award — not for a robot car this time, but for autonomous, robotic doctors.

Robots have been found in the operating suite since the 1980s for things like holding a patient's limbs in place, and later for laparoscopic surgery, in which surgeons can use remote-controlled robot arms to operate on the human body through tiny holes instead of huge cuts. But for the most part these robots have been, in essence, just very fancy versions of the scalpels and forceps surgeons have been using for centuries — incredibly sophisticated, granted, and capable of operating with incredible precision, but still tools in the surgeon's hands.

Despite many challenges, that is changing. Today, five years after that award announcement, engineers are taking steps toward building independent machines that not only can cut or suture, but also plan those cuts, improvise and adapt. Researchers are improving the machines' ability to navigate the complexities of the human body and coordinate with human doctors. But the truly autonomous robotic surgeon that the military may envision — just like truly driverless cars — may still be a long way off. And their biggest challenge may not be technological, but convincing people it's OK to use them.

Navigating unpredictability

Like drivers, surgeons must learn to navigate their specific environments, something that sounds easy in principle but is endlessly complicated in the real world. Real-life roads have traffic, construction equipment, pedestrians — all things that don't necessarily show up on Google Maps and which the car must learn to avoid.

Similarly, while one human body is generally like another, children's movies are right: We're all special on the inside. The precise size and shape of organs, the presence of scar tissue, and the placement of nerves or blood vessels often differ from person to person.

"There's so much variation in the individual patients," says Barbara Goff, a gynecologic oncologist and surgeon-in-chief at the University of Washington Medical Center in Seattle. "I think that that could be challenging." She's been using laparoscopic surgical robots — the kind that don't move on their own but do translate the surgeon's movements — for more than a decade.

The fact that bodies move poses a further complexity. A few robots already display some amount of autonomy, with one of the classic examples being a device with the (maybe-a-bit-on-the-nose) name ROBODOC, which can be used in hip surgery to shave down bone around the hip socket. But bone's relatively easy to work with and, once locked into place, doesn't move around much. "Bones don't bend," says Aleks Attanasio, a research specialist now at Konica Minolta who wrote about robots in surgery for the 2021 Annual Review of Control, Robotics, and Autonomous Systems. "And if they do, there's a bigger problem."

Unfortunately, the rest of the body isn't as easy to lock in place. Muscles contract, stomachs gurgle, brains jiggle, and lungs expand and contract, for instance — even before a surgeon gets in there and starts moving things around themselves. And while a human surgeon can obviously see and feel what they're doing, how could a robot know if its scalpel is in the right place or if tissues have shifted?

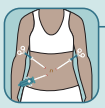
One of the most promising options for such dynamic situations couples the use of cameras and sophisticated tracking software. In early 2022, for example, researchers at Johns Hopkins University used a device called the Smart Tissue Autonomous Robot (STAR for short) to sew two ends of severed intestine back together in an anesthetized pig — a potentially very jiggly task — thanks to this visual system.

TIMELINE OF PROGRESS IN SURGICAL ROBOTS

1970s NASA explores telesurgery.

1983 First robot in the surgical suite, used to move patient's limbs into position during orthopedic surgery.

1985 First instance of a surgical robot, used during brain biopsy to avoid errors from hand tremors.



1985 First laparoscopic procedure.

1990s Laparoscopic surgery becomes more common, many novel procedures carried out and many new systems invented.

1991 First telepresence system, means surgeons don't need to be directly next to patient.

1992 First robot with task autonomy gets FDA approval. Used in hip replacement, ROBODOC can carry out certain pre-programmed tasks autonomously once initiated by a human.

2000s Surgical robots for general use become more common.

2000 Introduction of da Vinci, the first robotic system for general and laparoscopic surgery in humans.

2001 Doctors in New York City use telesurgery to operate on a patient in France.

2001 First robot with conditional autonomy gets FDA approval. Used in radiation therapy, CyberKnife can perform procedure autonomously.

2001 – present Refinement of existing surgical robots continues to expand, robots become smaller, lighter, easier to use, and offer more assistance features for surgeons.

2009 Steerable catheters to access and operate constrained regions not reachable with rigid laparoscopy.

2022 STAR robot successfully sutures severed pig intestine.

The future Surgical robots gradually acquire increasing autonomy.

Source: **Reporting by J Gaines**

A human operator tags the ends of the intestine with drops of fluorescent glue, creating markers the robot can track (a bit like an actor wearing a motion-capture suit in a Hollywood movie). At the same time, a camera system creates a 3-D model of the tissue using a grid of light points projected onto the area. Together, these technologies allow the robot to see what is in front of it.

"What's really special about our vision system is that it allows us to not only reconstruct what that tissue looks like, but it also does so fast enough that you can do it in real time," says STAR system codesigner Justin Opfermann, an engineering PhD student at Hopkins. "If something does move during the surgery, you can detect and follow it."

The robot can then use this visual information to predict the best course of action, presenting the human operator with different plans to choose from or checking in with them in between sutures. In tests, STAR worked well on its own — though not perfectly. In total, 83 percent of the sutures could be done autonomously, but the human still had to step in the other 17 percent of the time to correct things.

"The 83 percent can definitely be overcome," says Opfermann. Most of the problem was that the robot had a little trouble finding the right angle at certain corners and needed a human to nudge it into the right spot, he says. Newer, yet-to-be-published trials now have success rates in the high

90s. In the future, the human may only need to approve the plan, then watch it go, no intervention needed.

Passing the safety test

For now, though, there still needs to be someone in the driver's seat, so to speak. And it might be that way for a while for many different autonomous robots: While we could theoretically hand over complete decision-making to the robot, this does raise a question — one that has also plagued driverless cars.

"What happens if some of these activities go wrong?" says Attanasio. "What if the car has an accident?"

The general view, for now, is that keeping the humans ultimately in control is best — at least in a supervisory role, reviewing and signing off on procedures and standing by in case of emergency.

Even so, proving to hospitals and regulators that autonomous robots are both safe and effective may be the single biggest roadblock to truly human-free robots entering the surgical suite. Experts have a few takes on how to get around this.

For instance, designers will likely need to be able to explain to regulators exactly how the robots think and decide what to do next, says Attanasio, especially if they progress to the point where they're not just assisting a human surgeon but arguably practicing medicine themselves. That explanation may be easier said than done, though, since current artificial intelligence systems may leave observers few hints of how they make decisions. As a result, engineers may want to design with "explainability" in mind from the beginning.

Pietro Valdastri, a biomedical engineer at the University of Leeds in England and one of Attanasio's coauthors, thinks it's possible that no manufacturer will be able to easily solve the regulatory question, though he does have a work-around. "The solution here is to make a system that even if it's autonomous, it's inherently safe." This means the next generation of surgical robots may not resemble roadsters so much as bumper cars.

Valdastri is working on what are known as soft robots, particularly for colonoscopies. Traditionally, a colonoscopy requires snaking a flexible tube with a camera — an endoscope — through the intestine to look for early signs of colon cancer. The procedure is recommended for anyone over the age of 45 — but it can take a long time and a lot of training for an operator to become proficient with the endoscope. With few properly trained operators to go around, waitlists have ballooned.

But using a smart robot that can steer itself would make the job much easier — like driving a car in a video game, Valdastri says. The doctor could then focus on the matter at hand: spotting early signs of cancer. And in this case, the robot, created from soft materials, would be inherently safer than more rigid devices. It may even reduce the need for anesthesia or sedation, says Valdastri, since it could more easily avoid pushing against the intestinal walls. And with no way for the robot to cut or zap anything on its own, it may be easier for regulators to accept.

As the technology develops, Opfermann suggests, autonomous robots may start out getting approval only for simpler tasks, such as holding a camera. As more and more of these basic jobs get approved, the tasks may build up into an autonomous system. In cars, we first got cruise control, he says, but now there's brake assist, lane assist, even assisted parking — all of which build towards something driverless.

"I think this will be kind of similar," says Opfermann, "where we see small, autonomous tasks that eventually get chained together into a full system."

"The solution here is to make a system that even if it's autonomous, it's inherently safe." This means the next generation of surgical robots may not resemble roadsters so much as bumper cars.

Interesting Presentations of Primary Syphilis

Primary syphilis is a form of early syphilis developing 9 to 90 days after exposure. It usually takes typical, easily-recognizable clinical forms, including non-tender and non-itchy chancres on the genitals, which may be accompanied by regional lymphadenopathy. Two cases are reported with different presentations, one mimicking innocuous balanitis and the other a probable herpetic genital eruption.

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Abstract

Primary syphilis is a form of early syphilis developing 9 to 90 days after exposure. It usually takes typical, easily-recognizable clinical forms, including non-tender and non-itchy chancres on the genitals, which may be accompanied by regional lymphadenopathy. However, different presentations are being seen, which could cause diagnostic misses if a clinician lacks full awareness of these forms. Two cases are reported with different presentations, one mimicking innocuous balanitis and the other a probable herpetic genital eruption. The serology for both was positive and led to the correct treatment.

Keywords:

Balanitis, Follmann, Chancre

INTRODUCTION

Sexually-transmitted diseases are commonly encountered in present-day society due to varying lifestyle habits and the modern-day stresses of life. Despite education on safe sex practices, individuals at times engage in promiscuous and high-risk behaviour, resulting in the resurgence of sexually transmitted diseases. Of late, the clinical appearance of sexually transmitted disorders have been changing, and cases may not necessarily conform to typically known forms.

CASE REPORT

Case 1.

A 23-year-old circumcised male reported with a mildly painful reddish lesion on the glans penis, appearing about a week before presentation. He had used fucidin ointment, following which it became red all over with mild discomfort. Friction with undergarments gave rise to mild pain in the area. He did give a history of exposure to his 'girlfriend' one month prior to onset of symptoms, which was unprotected. The history of exposure was forthcoming only during the second review visit.

A clinical examination revealed uniformly erythematous erosive balanitis, which was mildly tender (Fig 1). No induration, chancre or discharge was present. No significant regional lymphadenopathy was present. No lesions were seen on other areas of the body. The initial appearance mimicked allergic contact dermatitis to fucidin ointment. The patient did not respond to treatment with mild topical steroid for suspected allergic contact dermatitis.

During the review of the case, when there was no response to topical steroid and the positive exposure history was forthcoming, serological screening for syphilis was requested. The serology for syphilis was reactive with a titre of 1:512. A confirmatory test for syphilis by TPHA revealed a positive titre of 1:5120.

A diagnosis of Syphilitic balanitis of Follmann (SBF) was made, and the patient treated with a single dose of Inj Benzathine Penicillin 2.4 Mega units, with good recovery.

Case 2.

A 41-year-old male presented with a mildly painful nodular eruption on the ventral aspect of penis near the frenulum of one-week duration. He gave a history of unprotected exposure three months prior, to his steady girlfriend.

Clinical examination revealed a firm, indurated nodule on the ventral aspect of the penis, with pseudo-vesiculation on the surface of the nodule (Fig 2). There was mild tenderness near the frenum of the penis, probably due to associated lymphangitis. There was no significant regional lymphadenopathy.

The patient was initially treated for probable herpes genitalis, due to the pseudo-vesicular lesions on the penile lesion. There was no significant improvement in the lesion from the antiviral therapy. On review, a serological test for syphilis was ordered, which showed reactive serology with a titre of 1:266. A diagnosis of early primary syphilis was made. The patient was treated with Inj Benzathine Penicillin 2.4 mega unit IM single dose, with subsequent subsidence of the lesion.

Figure 1: Erosive syphilitic balanitis of Follmann

Figure 2: Nodular lesion on the penis with pseudo-vesicular appearance

DISCUSSION

Eugène Follmann first described syphilitic balanitis as a manifestation of primary syphilis in 1948. Since then, it has been known as syphilitic balanitis of Follmann (SBF). Follmann recorded an incidence of balanitis in cases of primary syphilis of 0.3–0.5% (1). Thus, SBF should be considered an uncommon condition. Cardboard-like induration of the glans penis is described as a hallmark of SBF in a series of cases by Abdennader et al (2). However, this was not noted in the cases by Follmann. A chancre was also associated with one of their cases, and has been said to occur before, simultaneously with, or after balanitis. There was no induration or chancre in the present case with associated balanitis. Hence, a syphilis serology is warranted in all cases of atypical balanitis.

Syphilis can mimic many other diseases, and in the second case it resembled herpes genitalis, with some pseudovesicles on the skin surface of an indurated nodule on the ventral aspect of the penis. The indurated nodule can be explained by lymphangitis associated with the infection. Awareness of such presentation can facilitate early diagnosis of primary syphilis, especially if the genital lesion is atypical, as it was in this case.

In conclusion, syphilis serology is warranted for all indurated genital lesions, irrespective of clinical appearance, and in cases which do not respond to other treatments. Syphilis should also be suspected in cases of erythematous balanitis which are not itchy and are associated with a history of exposure.

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A Mountain and a Molehill: Report of Two Cases of Ectopic Pancreas

The presence of pancreatic tissue away from its normal location, in various places throughout the gastrointestinal tract, is known as ectopic pancreas, or pancreatic rest. It is usually an incidental finding and clinically silent.

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Abstract

The presence of pancreatic tissue away from its normal location, in various places throughout the gastrointestinal tract, is known as ectopic pancreas, or pancreatic rest. It is usually an incidental finding and clinically silent. Rarely, an ectopic pancreas can become inflamed or develop bleeding, obstruction or cancer. At times it may be challenging to diagnose. We would like to present two cases that demonstrate how variable the clinical presentation can be.

Keywords:

Ectopic pancreas, gastrointestinal stromal tumor (GIST), Leiomyoma.

INTRODUCTION

Ectopic pancreatic rest was first reported associated with an ileal diverticulum in 1727[1].

It is defined as pancreatic tissue with no anatomic or vascular connection with the main pancreas. The stomach and small intestine are the most common sites, but it has been reported at other sites as well. It is usually asymptotic unless it becomes inflamed or obstructed, or there is bleeding or malignant change[4]. We report two cases with contrasting presentations in this article.

Case report 1:

A 28 year-old male presented with melena, dizziness and intermittent abnormal pain of 3 day duration. The patient had moderately severe anaemia secondary to blood loss. The physical examination was normal. A blood test showed Hb of 8.7 mg/dl on CBC, but other routine blood tests including a liver function test and abdominal ultrasound were unremarkable.

Esophagogastroduodenoscopy (figure 1) revealed a globular polyploid mass in the distal corpus along the greater curvature, with a firm stalk; the overlying mucosa looked normal except for an ulcerated punctum. This was initially thought to be GIST/Leiomyoma.

A biopsy revealed lobules of pancreatic exocrine and endocrine components in the submucosa, with no evidence of malignancy.

TREATMENT

As the lesion presented with a significant upper GI bleed, a decision was made to transfuse 1 unit of blood PRBC and to proceed with laparoscopic surgery. During surgery, a gastric lesion was located through endoscopic transillumination. Gastrotomy was performed including a wide excision of the polyp with a 1 cm margin. Hemostasis was achieved and the gastrotomy closed. The patient had no postoperative complications and was discharged 4 days later. Surgical pathology was consistent with an ectopic pancreatic rest. The patient appeared well and asymptomatic during follow up.

Case report 2:

A 34 year-old male presented to the GE clinic with a 9 month history of recurrent dyspepsia. The physical

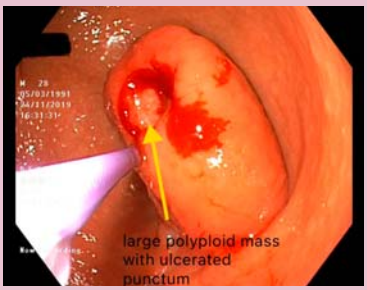

Figure 1: Esophagogastroduodenoscopy image of stomach. Case 1

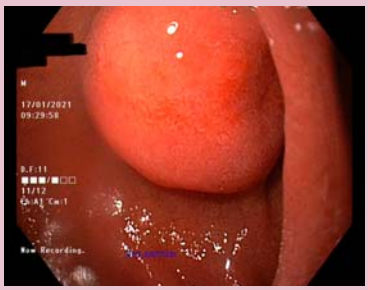

Figure 2: Esophagogastroduodenoscopy image of duodenum. Case 2

examination was clinically normal, and all routine blood tests including lipase, ultrasound abdomen, ECG, stress ECHO and TMT were unremarkable.

Esophagogastroduodenoscopy (figure 2) revealed one polypoidal lesion of around 1.5 cm at the D1/D2 junction, with normal overlying mucosa. The minor papilla appeared prominent but otherwise normal.

Endoscopic ultrasound (Figure 3) showed a 15.76 mm x 10.31 mm heterogeneous, predominantly hypo-echoic, polypoidal, regular, oval shaped lesion, probably arising from the muscularis propria. The mucosa/ muscularis mucosae/ submucosa/serosa appeared to be normal and were not involved with the hypo-echoic lesion. Using a 22 gauge EchoTip/procore Cook needle, a fine needle aspiration (FNA) biopsy of the lesion was performed. This confirmed the presence of heterotopic pancreatic parenchyma, with pancreatic ducts and acinar cells with pink zymogen granules (figure 4).

Treatment:

As this lesion was an incidental finding, and its contribution to the patient's symptom of functional dyspepsia was rather untenable, no further action was advised.

DISCUSSION

Ectopic pancreas is defined as pancreatic tissue with no anatomical or vascular connections with the normal body of the pancreas [3]. It is reportedly more common in males, usually aged 30 to 50 years. Variable incidence of 0.5-13.7% has been reported in autopsies[3].

Heterotopic pancreatic tissue is morphologically and physiologically identical to pancreatic tissue[4]

Classification:

Gaspar-Fuentes classified heterotopia of the pancreas into four types. Type I heterotopia consists of normal pancreatic parenchyma, sucha as acini, ducts, and islet cells. Type II heterotopia (canalicular type) only includes pancreatic ducts. Type III heterotopia is comprised of only exocrine acinar tissue. Type IV heterotopia includes only endocrine islet cells[6].

Theory of development:

- The pancreas develops from many evaginations inside the wall of the primordial duodenum; some of these evaginations fail to migrate to their normal place and give rise to ectopic pancreatic tissue[5]. Pancreatic metaplasia of the endodermis in the gastric submucosa during embryogenesis is proposed in a separate theory[5].

Location:

- 25-38% of cases have ectopic pancreatic tissue in the stomach, 17-36% in the duodenum and 15-21.7% in the jejunum. It is rarely observed in the esophagus, common bile duct, gallbladder, mesentery, spleen, mediastinum and fallopian tubes. The antrum is the most common location in the stomach, observed in 85-95%, of cases with heterotopic tissue in the stomach, especially along the greater curvature[5]. The gastric submucosal layer is the most commonly involved, followed by the muscularis and subserosal layers. In the presented cases, the pancreatic tissue involved the submucosa in case 1 and the muscularis propria in case 2.

Sign and symptoms:

- This condition is usually asymptotic, but complications such as acute or chronic pancreatitis, abscess and pseudocyst formation can occur.
- Pain may occur due to inflammation of the pancreatic tissue[9].
- Mucosal erosion, ulceration and perforation can lead to a GI bleed, especially in the small intestine.[8]
- Formation of a pre-pyloric mass can cause gastric outlet obstruction. Other unusual presentations include obstructive jaundice due to bile duct obstruction[8]. Usually lesions bigger than 1.5 cm in size are more likely to cause clinical symptoms[8].
- Carcinoma can rarely develop[10]. Heterotropic pancreatic cancer

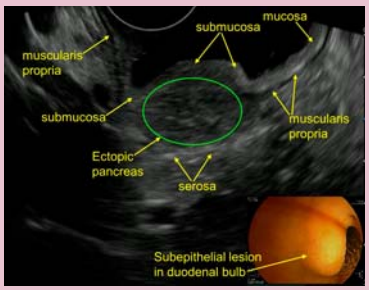

Figure 3: Endoscopic ultrasound image of duodenum. Case 2

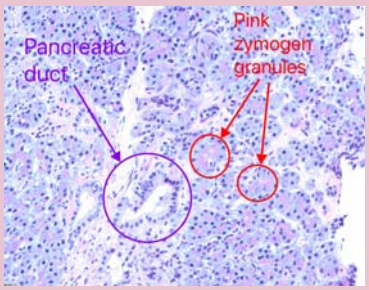

Figure 4: Histopathological image of biopsy of polypoidal mass. Case 2

must be located inside or close to the ectopic pancreas, with a transition zone between the pancreatic tissue and the cancerous neoplasm. The acini and ducts should make normal pancreatic tissue[7]. Ectopic pancreas adenocarcinomas have a favorable prognosis compared to pancreas cancers[10].

Diagnosis and management:

Upper GI endoscopy typically reveals an umbilicated subepithelial lesion. Diagnosis may be confirmed by biopsy[10]. Computed tomography lacks specificity in diagnosing ectopic pancreatic tissue as it cannot differentiate ectopic pancreas and other submucosal neoplasms[11].

Endoscopic ultrasonography can detect submucosal rests of 0.5-2 cm in size and allows fine-needle aspiration for cytologic evaluation with 80%-100% sensitivity[11].

In this report, both cases were diagnosed histologically. An endoscopic biopsy was positive for case 1, and subsequently confirmed by surgical excision. Case 2 was diagnosed with EUS guided biopsy. An intra-operative frozen section can help in differentiating pancreatic heterotopia from gastrointestinal autonomic nerve tumour, gastrointestinal stromal tumour (GIST), lymphoma, carcinoid tumour or even gastric cancer. Surgical resection is curative in most cases.

CONCLUSION

Pancreatic heterotopia/ectopic pancreas is one of the differential diagnoses of extramucosal gastrointestinal lesions. Clinical presentation may vary from an asymptomatic incidentally detected lesion to catastrophic GI haemorrhage leading to anaemia and even cancer.

It can be challenging to diagnose, especially when located entirely submucosally. Endoscopic ultrasound (EUS)-guided biopsy can help to make a confident diagnosis in most cases. Surgery is the definitive treatment, but may only be required in a minority of cases.

List of abbreviations

CT computer tomography
ECG electrocardiogram
ECHO echocardiogram
EUS endoscopic ultrasound-guided
FNAC fine needle aspiration cytology
GIST gastrointestinal stromal tumor.
GI gastrointestinal
TMT treadmill test

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Case Report

Thrombotic Thrombocytopenic Purpura (TTP) – a Rare Presentation with COVID-19

Thrombotic thrombocytopenic purpura (TTP) is a rare haematological disorder which can be hereditary or acquired. Hereditary TTP is a rare autosomal recessive disorder, caused by mutations in gene ADAMTS13, which result in the absence or severe deficiency of the plasma metalloprotease ADAMTS13.

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Keywords:

COVID-19, Thrombotic thrombocytopenic purpura, plasma exchange, ADAMTS13

ABSTRACT

A 22-year-old female with no previous morbidities presented with acute onset neurological symptoms in the form of hemi-sensory phenomena. On evaluation, she had fever. Routine COVID-19 RT-PCR testing proved to be positive. During the course of hospital stay, the patient developed classical features of acquired TTP. Her ADAMTS13 level was 36% of normal activity, which is suggestive of direct, viral-mediated thrombotic microangiopathy. High VWF levels and low ADAMTS13 activity have both previously been reported with SARS-Cov-2 infection. In rare cases like ours, this can mimic classical TTP.

ABBREVIATIONS

TTP – Thrombotic thrombocytopenic purpura; COVID-19 – Coronavirus disease 2019; ADAMTS13 – A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; VWF – von Willebrand factor; HUS – Haemolytic uremic syndrome; RT-PCR – Real time reverse transcriptase polymerase chain reaction; MAHA – Macroangiopathic haemolytic anaemia; LDH – Lactate dehydrogenase; ANA – Antinuclear antibody; ELISA – Enzyme-linked immunosorbent assay; PLEX – Plasma exchange; TMA – Thrombotic microangiopathy; SARS-CoV2 – Severe acute respiratory distress Coronavirus 2.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare haematological disorder which can be hereditary or acquired. Hereditary TTP is a rare autosomal recessive disorder, caused by mutations in gene ADAMTS13, which result in the absence or severe deficiency of the plasma metalloprotease ADAMTS13. Immune-mediated ADAMTS13 deficiency (iTTP) is most frequently acquired via ADAMTS13

auto-antibodies. Half of all iTTP cases present secondary to clinical conditions such as bacterial infections, systemic lupus erythematosus (SLE), Anti-phospholipid syndrome, pregnancy, drugs, pancreatitis, HIV infection, cancers and organ transplantation. Co-presentation of COVID-19 related thrombotic microangiopathy with TTP and haemolytic uremic syndrome (HUS) has been described in the literature (1-6). We report a case of TTP in a young female in the setting of SARS-Cov-2 infection.

CASE REPORT

A 22-year-old, previously healthy, obese female presented with sudden weakness and numbness of the right side of her body. She also had slurring of her speech and facial deviation which resolved within a few hours. The patient did not report fever, anosmia, and cardio respiratory or gastrointestinal symptoms. There was no recent exposure to drugs. The family history was negative and there was no history of any illness during childhood. On evaluation in the emergency room, the patient's readings were as follows- temp 38'C, HR 100/min, BP 120/80 mmHg, RR 12/min. Pallor was noted. No lymph nodes or purpura were seen. A neurological examination showed power of 5/5 for all of the limbs. There were no sensory, cranial nerve or cerebellar deficits. The rest of the systems were normal on examination.

In view of the pandemic setting, a nasopharyngeal swab was taken which tested positive for COVID-19 by RT-PCR. Laboratory investigations revealed anaemia, thrombocytopenia, unconjugated hyperbilirubinemia, and elevated reticulocyte count (18%) (Table 1). A peripheral smear showed normocytic anaemia, thrombocytopenia and schistocytes (12%), consistent with microangiopathic haemolytic anaemia (MAHA). Coagulation parameters including fibrinogen, PT-INR and APTT were normal. LDH and D-Dimer were both markedly elevated. Direct and indirect Coombs' tests were negative. Serum C3 and C4 were normal. Troponin was also normal. ANA by ELISA and antiphospholipid antibody IgM results were negative. The automated blood cultures were sterile. Serology test results for HIV, Hep B, Hep C and Dengue viruses were also negative. A rapid malarial antigen test was negative.

Urinalysis revealed trace albuminuria and microhaematuria. The renal function was normal. Liver function showed mild elevation of SGOT. A bone marrow examination was consistent with peripheral platelet destruction. Radiological investigations revealed a normal chest X ray. MRI and MRV-Brain results were also normal. ADAMTS13 testing revealed 36% of normal activity. An inhibitor assay was not available.

A diagnosis of TTP was made and the patient was started on IV methyl prednisone and plasma exchange. She received daily plasma exchanges of 2-2.5 litres, with replacement using fresh frozen plasma. She had only minimal symptoms of COVID-19. After 3 sessions of PLEX, the patient's haematological parameters started improving. Her neurological symptoms also improved. Rituximab was not given in view of COVID-19. She showed a good response and achieved remission. The patient was discharged on oral prednisone. A COVID-19 antigen test was negative on day 10 post-admission. She has not shown any signs of relapse after discharge.

DISCUSSION

TTP can be hereditary or acquired, characterised by deficiency of ADAMTS13, a polymer which degrades multimers of von-Willebrand factor. ADAMTS13 deficiency is most frequently acquired via ADAMTS13 auto antibodies, but rarely inherited via mutations of the ADAMTS13 gene. Hereditary TTP usually presents in childhood and has a relapsing tendency. The first episode of TTP most commonly occurs during adulthood (90% of all TTP cases). In 50% of the cases, another clinical condition triggers the onset of TTP. Well-described triggers include bacterial infections, SLE, pregnancy, drugs, HIV infection and organ transplantation. In 50% cases the trigger remains `idiopathic`.

SARS-Cov-2 infection & COVID-19 vaccination have been reported to cause thrombocytopenia & macrothrombosis (1). Thrombotic microangiopathy involving the lungs and kidneys are also described. SARS-CoV-2 causes endothelial injury by binding to ACE-2 receptors expressed in the vascular endothelial cells. Generation of auto-antibodies to ADAMTS13 leads to TTP (2). Other suggested potential mechanisms include elevated VWF factor and low ADAMTS13 activity. Both have been reported to predict development of TMA in COVID-19 (3).

As of April 2021, varying presentations ranging from 'Classical TTP' to 'TTP-like illness of COVID-19' numbering fewer than 20 cases have been reported in the literature. Two case reports with clinical features consistent with TTP in the setting of COVID-19 infection have been reported (4). ADAMTS13 levels are not provided for either of those cases. However, very low ADAMTS13 activity and positive inhibitor leading to iTTP have been reported by Albiol-et-al (2). Law-et-al report that COVID-19 infection can trigger autoimmune haemolytic anaemia & iTTP (5). A case series from Iran reported 4 patients with classical clinical and haematological parameters consistent with classical TTP during COVID-19 infection (6). COVID-19 infection has also been reported to trigger

Table 1. Etiological work-up

CBC	**Haemoglobin**	**6 g/dL**
	Total count	15,000 cells/cu.mm
	Platelet count	13,000 cells/ cu.mm
	MCV	88.3 fL
Hemolysis work-up	Direct Coombs' test	
Negative		
	Indirect Coombs' test	
Negative		
	LDH	3918 U/L
	Reticulocyte count	18 %
	Total Bilirubin	4.5 mg/dL
	Direct Bilirubin	0.7 mg/dL
Renal function	Urine microscopy	Albumin 1+, RBC 50 cells/hpf
	Urea	20 mg/dL
	Creatinine	0.6 mg/dL
Coagulation Profile	D-dimer	6262 ng/mL
	PT-INR	1.05
	aPTT	26.2 seconds
	Fibrinogen	399 mg/dL
Serology	ESR	62 mm 1st hour
	CRP	23.2 mg/L
	ANA (EIA)	Negative
	Phospholipid antibody IgM	Negative
	Serum C3, C4	Normal
	HIV 1 & 2	Non-reactive
	HCV	Non-reactive
	HBsAg	Non-reactive
Infection work-up	Ferritin	1081 ng/mL
	Procalcitonin	0.06 ng/mL
	Blood c/s	Sterile
Malignancy work-up	Bone marrow study	Normal
Imaging	Chest X-Ray	Normal
	MRI Brain and MRV	Normal
ADAMTS13		
	36% of normal activity (low)	

anti-phospholipid antibodies leading to thrombosis and thrombocytopenia. COVID-19 infection has been reported to cause high von Willebrand Factor (vWF) levels with low ADAMTS 13 activity which may lead to the development of thrombotic microangiopathy (3).

In our case, female gender, obesity and COVID-19 were the only risk factors for TTP. Both the clinical and haematological parameter features were classical of TTP. ADAMTS13 activity being 36% of normal raises the question of whether this is mechanistically more like 'TTP-like illness of COVID-19' rather than acquired iTTP, in which ADAMTS13 activity falls to <10%. An increased incidence of young stroke in COVID-19 has been reported. Possible mechanisms include a hypercoagulable state resulting from systemic inflammation, cytokine storm and direct viral-induced endothelial damage leading to cerebral arterial and venous thrombosis (3). TTP should be considered in young individuals with COVID-19 and neurological symptoms.

CONCLUSION

SARS-Cov-2 infection is emerging as a strong risk factor for the development of thrombotic microangiopathy. 'COVID-19 induced TTP' is likely a spectrum ranging from classical iTTP (<10% ADAMTS13 activity and anti-ADAMTS13 antibodies in plasma) to COVID-19 induced TTP (direct endothelial damage leading to a high VWF/ADAMTS13 ratio). Plasma exchanges and steroids have shown anecdotal benefit in all reported case series. The role of Rituximab remains unclear. Neurological and haematological parameters have shown sustained improvement with a lower reported relapse rate than classical immune TTP, suggesting a strong causative role for COVID-19.

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UHL's Anomaly: A Rare Form of Congestive Cardiac Failure in Early Childhood

UHL's anomaly is a rare congenital anomaly of the heart in which there is a congenital absence of the right ventricular myocardium. Only a few cases have been reported in the literature. Two cases of children with Uhl's anomaly who presented with this rare condition and are under medical management.

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UHL's anomaly; congestive cardiac failure; right ventricle; myocardium; right ventricular dysfunction.

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ABSTRACT

Uhl's anomaly is a rare congenital anomaly of the heart in which there is a congenital absence of the right ventricular myocardium. Only a few cases have been reported in the literature. It normally presents in infancy with features of congestive cardiac failure; however, cases have been reported in adults with right heart failure. Although the prognosis is not good, palliative surgical modalities are being performed in the Indian population. We report below two cases of children with Uhl's anomaly who presented to us with this rare condition and are under medical management.

INTRODUCTION:

Uhl's anomaly is a rare form of congenital right ventricular cardiomyopathy which is characterized by the partial or complete absence of the right ventricular myocardium. The epicardium and endocardium of the right ventricle are opposed, but the septum and papillary muscles of the right ventricle are normally muscularized. The condition is mainly sporadic, though some familial occurrences are present in the literature. About a century ago, Ostler[1] described a "parchment heart", but the first case was officially reported in 1952 by Henry Stephen Mc Graw Uhl.[2] It is such a rare condition that until 1993 only 84 cases were reported, as summarized in a systemic review by Gerlis.[3] A close differential diagnosis of this condition is arrhythmogenic right ventricular dysplasia (ARVD). We present the cases of two children who presented to us with this rare anomaly and are under medical management.

CASE 1:

An 8-month old, apparently asymptomatic male child was referred from an outside hospital as a case of pulmonary atresia, having presented there with excessive crying and breathing difficulty with

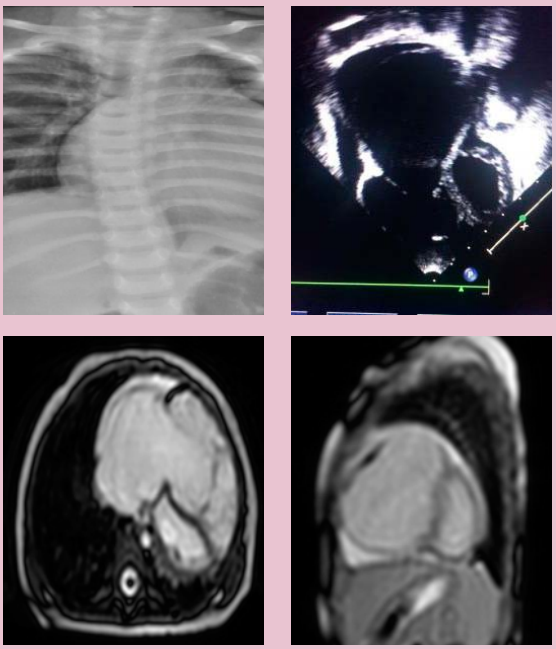


Figure 1. A: CXR showing cardiomegaly; B: 2D Echo showing dilated RA and RV; C and D: CMR images showing dilated RA, RV with thin RV free wall.

mild cyanosis. On examination, the child had a heart rate of 106/ min, regular, BP: 98/58mm Hg, RR: 28/min with no retractions, Spo2: 90% room air. The cardiac apex was in the 4th intercostal space, 0.5 cm lateral to the midclavicular line. The first sound was normal in intensity and duration, and the second heart sound had normal split and intensity. A soft pan systolic murmur of 2/6 intensity was heard at the lower left sternal border. Soft, non-tender hepatomegaly of 1 cm was present, with no splenomegaly. CXR revealed massive cardiomegaly. ECG showed sinus rhythm with right atrial enlargement. An echocardiogram revealed a dilated right atrium, and ventricles with a thin right ventricular lateral wall. The leaflets of the tricuspid valve were non-coapting and thence, there was severe low-pressure tricuspid regurgitation. Severe RV dysfunction was observed. The left ventricle had normal function.

Due to suspicion of Uhl's anomaly, cardiac magnetic resonance (CMR) imaging was performed, which confirmed Echo findings of dilated RA, RV (RVEDV-123ml/m2) with severe tricuspid regurgitation. There was poor right ventricular function (RV EF-15%), with a thin free wall with flattened inter-ventricular septum during diastole. There was no evidence of fibro-fatty RV wall infiltration, thus ruling out ARVD.

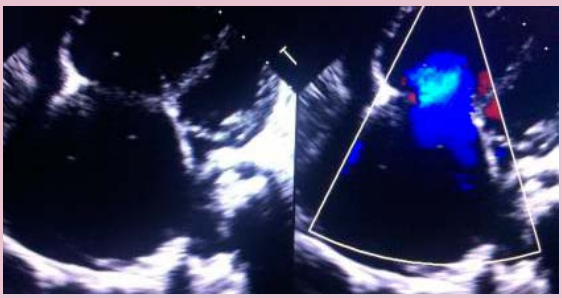
On delayed enhancement imaging, we observed enhancement along the RV free wall, apical RV, and RV portion of the distal IVS (Fig: 1). Minimal pericardial effusion was present. The CMR findings confirmed Uhl's anomaly, and the parents were counselled about the management options. They did not prefer surgical palliation. The child was discharged on diuretics and ACE inhibitors and is in follow up without any symptoms presently.

CASE 2:

A 2-year-old, apparently asymptomatic boy was referred to us with an incidental murmur. On examination, his vitals were normal with HR: 98/mins regular, RR-20/min, BP: 102/64 mm Hg, saturation in room air: 94%. The apex was in the 5th intercostal space, 1 cm lateral to the midclavicular line. The first heart sound was normal in intensity and duration and the second heart sound was normal in intensity with normal splitting. A soft systolic murmur was present at the left lower sternal border. CXR showed mild cardiomegaly. Echocardiography showed dilated RA and RV, with severe tricuspid regurgitation and right ventricular dysfunction. A diagnosis of organic TR was made, diuretics were started and the child was placed under follow up. The child developed features of congestive heart failure. CMR imaging showed dilated RA and RV, with a thinned out RV wall without any fatty infiltration of the RV wall, suggesting Uhl's anomaly (Fig: 2). The parents were informed about the condition and prognosis and they too preferred medical management over the palliative surgical procedure.

DISCUSSION

Uhl's anomaly is the congenital complete or partial absence of the right ventricular myocardium. There is no evidence of deposition of adipose tissue, inflammation or necrosis. Since the first description of Uhl's anomaly about 70 years ago, different theories have been proposed for this anomaly, although the exact cause still is not known. Initially, it was thought to occur due to embryologic failure of the right cardiogenic fold, which in turn leads to a congenital absence of the right ventricular myocardium. Apoptotic destruction of the myocardium after the heart has fully developed is a recent explanation which has been forwarded by some studies, including by



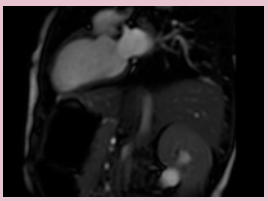


Figure 2. A: 2 Echo with colour showing dilated RA and RV, with colour doppler showing severe TR; B: CMR images showing dilated RA and RV, with thin RV free wall.

Uhl himself in 1996.[4] A potential genetic predisposition is also a possibility, as the anomaly has been described in twins and family members.[5,6]

In most cases, the anomaly presents in the early years of age with congestive cardiac failure.[3] Cyanosis is also not uncommon as a symptom. Cases have been reported in which Uhl's anomaly has presented with massive peripheral oedema or pleural effusion leading to cardiac tamponade.[7,8] It may rarely mimic other congenital cardiac anomalies like Ebstein's anomaly or even functional pulmonary atresia. [9,10] The baby in our first case was referred to us with a diagnosis of pulmonary atresia. The association of other congenital anomalies with Uhl's anomaly is relatively rare. The first diagnosis of Uhl's anomaly was made by Uhl on autopsy, but presently, with the advent of echocardiography and cardiac magnetic resonance (CMR) imaging, early diagnosis is possible.[11]

Arrhythmogenic right ventricular dysplasia (ARVD) is an entity closely related to this condition.[12] The characteristic feature of ARVD is fibrofatty tissue replacement of RV myocardium, whereas Uhl's anomaly has a complete absence of muscle in the parietal wall of RV (composed only of the opposing layers of endocardium and epicardium). The features of these two conditions overlap each other, so in 1993 Gerlis and co-workers enumerated certain features to differentiate between the 2 conditions.[3] The diagnosis of Uhl's anomaly is favoured due to the younger age of presentation, predominant features of cardiac failure, and lack of family history and other associated congenital heart diseases. Even in Uhl's anomaly, RV is known to be arrhythmogenic.

The prognosis of Uhl's anomaly is not good, therefore only palliative surgical procedures can be performed. The aim of surgical management of Uhl's anomaly is the alleviation of right heart failure by the complete exclusion of RV with bidirectional Glenn or Fontan connection, or a reduction plasty of RV combined with bidirectional Glenn (one and a half ventricle). Each of these palliative procedures is described as having good results nowadays.[13]

CONCLUSION

Uhl's anomaly is a rare cause of congestive heart failure in infancy, which can be diagnosed adequately by echocardiography and CMR. Early diagnosis will prevent the morbidity associated with this disease. Palliative surgical procedures are increasingly being performed around the globe, yet still the prognosis is poor.

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Case Report

Missed Opportunity to Suspect and Diagnose Infective Endocarditis at an Early Stage

The overall incidence of infective endocarditis is 3-10 per 100000 people, with a mortality rate of up to 30% at 30 days post-admission. Presentation can be unusual and diverse and can vary from person to person. A high index of clinical suspicion is required. A delay in diagnosis can be fatal.

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Infective endocarditis, Native valve endocarditis, Aortic stenosis, Streptococcus viridans

ABSTRACT

Infective endocarditis is a life-threatening medical condition that is not frequently encountered in routine clinical practice. The overall incidence of infective endocarditis is 3-10 per 100000 people, with a mortality rate of up to 30% at 30 days post-admission. Presentation can be unusual and diverse and can vary from person to person. A high index of clinical suspicion is required. A delay in diagnosis can be fatal.

Here we present a case of infective endocarditis. The patient was initially evaluated for anaemia in another hospital. No cause was found, and the case was treated as anaemia of unknown chronic disease. The patient came to our centre a few weeks later, and we were able to diagnose them with infective endocarditis. She was promptly referred and operated upon, but died in the post-operative period.

This case highlights the importance of early diagnosis and treatment before full-blown valve damage and cardiac failure ensues. A thorough history and clinical examination, in conjunction with careful selection of investigative modalities, is the only way to make an accurate diagnosis.

INTRODUCTION

Infective endocarditis (IE), first described by William Osler in 1885, is defined as an infection of the endocardial surfaces of the heart—primarily of the heart valves, the mural endocardium, or a septal defect. The intracardiac effects of IE include severe valvular insufficiency, intractable congestive heart failure and myocardial abscesses. If left untreated, IE is inevitably fatal.[1-3] IE occurs most frequently in patients with a damaged heart valve, a prosthetic valve, or a pacemaker

lead. Any structural heart disease can predispose a person to develop IE. The overall incidence of infective endocarditis is 3-10 per 100000 people, with a mortality rate of up to 30% at 30 days post-admission.[2-3] In the past, rheumatic heart disease was the main precursor to IE and it is still prevalent in developing countries.

The endocardium, which covers the heart valves, is the primary area affected by IE. If the infection remains untreated, it will damage the valves completely, resulting in congestive heart failure. Early diagnosis is key to improving clinical outcomes and survival. Antibiotics are the mainstay of treatment, but surgery may be required for some patients.

Staphylococcus aureus, Streptococcus viridans, Coagulase negative staphylococci, Enterococci and *Streptococcus bovis* are the most common organisms causing IE. *S. aureus* can produce acute infective endocarditis. Native valve endocarditis caused by S. aureus has a more aggressive course. Despite technological advances in diagnostic and therapeutic modalities, the overall mortality has not improved. Aortic valve infective endocarditis is still a life-threatening disease, which is associated with high mortality and morbidity.[2-3]

Table I. Modified Duke's criteria for IE[12,18]

Major criteria	1. Blood culture positive for typical microorganism* 2. Valvular vegetation seen on echocardiogram
Minor criteria	1. Predisposing cardiac lesion 2. Intrevenous drug use 3. Fever more than 38°C 4. Embolic phenomena 5. Immunologic phenomena such as glomerulonephritis 6. Positive blood culture not meeting above criteria
Diagnosis	Definite IE 2 major or (1 major + 3 minor) criteria Possible IE (1 major + 1 minor) or 3 minor criteria

*typical microorganism for IE from two separate blood cultures

CASE REPORT

A 75-Year-old Omani woman, with ongoing treated diabetes, hypertension and hypothyroidism, presented with a history of fever with duration of more than 3 weeks, along with chills, rigor, generalized body pain, arthralgia and severe fatigue. She had been investigated extensively in another hospital for severe anaemia, but no specific diagnosis had been established. The patient was treated with iron and erythropoietin injection, and a provisional diagnosis of anaemia of chronic disease was made.

There was no history of cough or breathlessness, but the patient had nausea and occasional episodes of loose stools. She had a history of significant weight loss. There was no history of any joint pains, rash or tremor, and no history of dental procedures. There was a history of documented high body temperature of more than 39°C on several occasions.

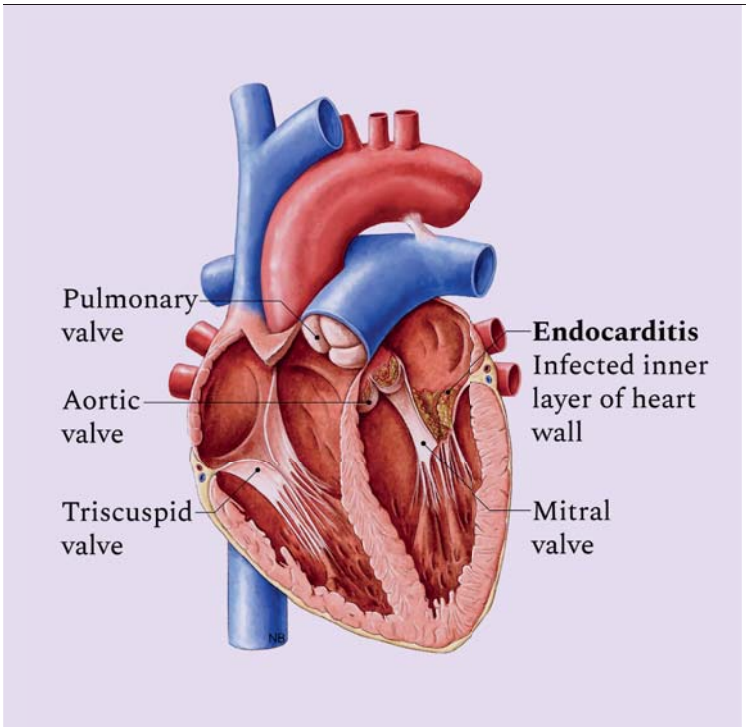
On examination, the patient looked ill and was pale. Her temperature was 39°C. She had a pulse rate of 90/minute and a blood pressure of 130/80mm Hg. A systemic examination revealed a Grade 3 ejection systolic murmur in the aortic area, and mild hepatomegaly. All other systems were within normal limits.

The clinical differentials considered at this point were a urinary tract infection (common in diabetics), enteric fever (prolonged fever with occasional loose stools), malignancy (consistent with an elderly lady with anaemia and body pain), Brucellosis (consumption of unpasteurized milk is common in the GCC), and infective endocarditis (in view of the pallor and cardiac murmur).

Laboratory investigations revealed a haemoglobin level of 6.9 g/dl and WBC of 7140/mm3, with differentials of 77% (neutrophils), 13% (lymphocytes) 8.8% (monocytes), 1.2% (eosinophils). Platelet count was 192 × 103/µl, and ESR 75 mm/hour. Urine microscopy showed pus cells 10-15/ Hpf. A Widal test was positive with titer of 1/320 for S. typhi O. A routine stool examination was normal, the patient's HIV status was negative and an IgM brucella test was also negative.

Though the Widal test was positive with significant titers and there were minimal pus cells in the urine, the clinical picture was not consistent with UTI or enteric fever. The fever was mild and enteric fever could not explain the chronic anaemia.

In view of the chronic anaemia, elevated ESR and cardiac murmur, the possibility of infective endocarditis was considered. A blood culture was performed, showing growth of a viridans Streptococcus species (S. mitis) on Vitek 2 Compact (Biomerieux), making infective endocarditis a distinct possibility. The isolated organism was sensitive to ampicillin, moxifloxacin, levofloxacin, tetracycline, doxycycline, vancomycin and linezolid, but resistant to clindamycin.



The patient was referred to another center for an echocardiogram (ECHO), which demonstrated severe aortic stenosis and mild aortic regurgitation with multiple vegetations on the aortic valve, extending up to the root of the aorta. The patient underwent surgery, but unfortunately succumbed post-operatively.

DISCUSSION

Infective endocarditis (IE) is an infection of the heart valves characterized by an aggregation of bacteria in a fibrin plaque known as 'vegetation'. The most common causative agents are the streptococci that are commensals of the oropharyngeal cavity. IE is treated based on blood culture report findings if positive, and empirically if negative.[1] The viridans streptococci, a heterogeneous group of alpha-haemolytic streptococci, is part of the normal flora of the mouth, and is responsible for dental caries and pericoronitis as well as subacute infective endocarditis.[5-6] The most relevant species clinically are Streptococcus oralis (mitis) and Streptococcus sanguis, which are responsible for 40-60% of endocarditis cases occurring on normal valves.[7] Speciating Streptococci has become much easier with the development of automated systems such as VITEK.

Although rarely associated with renal failure and septic shock, endocarditis caused by viridans Streptococci is commonly associated with peri-annular lesions (abscesses, pseudoaneurysms, or fistulas) or heart failure.[8] The risk of death is around 15%.

Although the viridans Streptococci are non-aggressive microorganisms, the associated valvular destruction is similar to that caused by other pathogens in that it causes left-sided endocarditis.[8]

The clinical presentation of IE has been traditionally classified as sub-acute and acute. Sub-acute IE presents as a prolonged low-grade fever for weeks, or even months, with other symptoms such as fatigue, chills, myalgia, and weight loss.[9-11] Fever may be minimal or even absent in patients with underlying debilitating illnesses such as chronic liver disease.[19] Acute IE, on the other hand, presents with high fever and rapidly deteriorates if not recognized early.[9,10] According to the modified Duke's criteria,[18] the diagnosis of infective endocarditis was supported by two major criteria that were met, namely positive blood cultures of viridans Streptococci and the identification of the vegetation, both echographically and intra-operatively. Laboratory abnormalities that can frequently be seen in IE include elevated acute phase reactants (erythrocyte sedimentation rate and C-reactive protein), anaemia, thrombocytopaenia, haematuria, and positive rheumatoid factor.[9,10] Cardiac echocardiography is essential for the diagnosis and for monitoring vegetation size and cardiac function. However, it is important to note that the absence of vegetation on echocardiography does not necessary rule out IE.

Three sets of blood cultures taken before starting antibiotics are likely to detect bacteremia in 98% of cases. Duke's criteria have an overall sensitivity of 80%, but this is significantly lower in prosthetic valve endocarditis and infections around implantable electronic devices. The sensitivity of Transthoracic Echocardiography (TTE) is around 70% for detecting vegetations on native valves, but this is reduced to 50% in prosthetic valve endocarditis and is lower in the case of implanted electronic devices. Transoesophageal echocardiography (TOE) has both sensitivity and specificity exceeding 90% for vegetations,[2] but initial studies may yield false negative results in 6-18% of cases[12]. Three-dimensional TOE may occasionally augment the findings of standard TOE. In addition, 18-fluorodeoxyglucose positron emission tomography may identify perivalvular or perigraft infections not seen with TOE[12].

The viridans streptococci, Staphylococcus aureus and enterococcus spp. together account for 80-90% of all

cases of IE[2]. A study conducted in 16,867 patients with infective endocarditis in Spain over the period 2003-2014, documents an increasing trend of infections with coagulase negative Staphylococcus and Enterococcus species[13]. S. aureus and the enterococci are associated with poorer outcomes[14]. Infections with unusual organisms including gram negative bacilli and fungi are often seen in intravenous drug users[15]. Duration of illness is found to be shorter in Staphylococcus infections and longer in the case of Streptococcus infections, and higher mortality is observed in infections with a shorter duration of illness.[16]

Even though antibiotic therapy is the mainstay of treatment, surgery may be needed in one third of patients during active illness, and in another third after the initial healing process.[17] A prognosis of infective endocarditis depends on several factors including age, comorbid conditions such as diabetes, delayed diagnosis, involvement of prosthetic valves or the aortic valve, antibiotic resistance etc.[12] In developed countries, the overall survival rate is 80-85%, however rates vary considerably among sub-populations of IE patients.[12] Overall survival rates after 1 year of successful treatment range from 80-90%.[12] Antibiotic prophylaxis before dental and surgical procedures to prevent IE was once very wide spread in clinical practice. However, due to lack of evidence, the American Heart Association and European Society of Cardiology now recommend prophylactic antibiotics only for those patients who are at a high risk of morbidity and mortality due to IE.[12]

CONCLUSION

As the frequency of IE in day-to-day practice is very low, and the presentation varies from person to person, if not suspected clinically, diagnosis may be missed or delayed. Clinical diagnosis depends upon proper history taking and examination. Infective endocarditis should always be suspected in a febrile patient, irrespective of cardiac status. The presence of anaemia with valvular heart disease significantly increases the probability of infective endocarditis. Timely and prompt diagnosis is very crucial. A late diagnosis may not help the patient, as in this case. Apart from the delay in diagnosis, she had other predictors of mortality, including diabetes, old age and aortic valve involvement. A history of fever is extremely important in the anaemia work-up, as this redirects the evaluation process. Fever in infective endocarditis may be low grade, and is often overlooked. If anaemia is associated with fever, a thorough clinical examination must be performed to make sure that a cardiac murmur is not missed.

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Case Report

Intra-operative Rendez-vous ERCP

Intra-operative rendez-vous ERCP : Applicability, safety and effect on hospital stay in patients with gallbladder and common bile duct stones. Initial experience from a private healthcare institution—Case Series.

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The authors have declared no conflict of interest.

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Keywords

Acute cholecystitis, pancreatitis, CBD calculus, laparoscopic cholecystectomy, Rendezvous ERCP, traditional ERCP.

Study design

Retrospective, non-randomized, observational, using historical control subjects.

Study population

Twenty-five consecutive patients with gallbladder and CBD calculi, for whom both ERCP and LC were considered clinically indicated, were recommended to receive joint LC and IOR-ERCP. Detailed informed consent was taken for both procedures. Their outcomes were compared with an equivalent number of patients who underwent conventional management.

ABSTRACT

This case series compares the traditional approach of endoscopic retrograde cholangiopancreatography (ERCP) with separate laparoscopic cholecystectomy (LC), versus combined LC and intra-operative rendezvous ERCP (IOR-ERCP). We consider the costs and benefits of each approach in terms of applicability, efficacy, safety, cost effectiveness and duration of hospital stay.

25 patients with cholelithiasis and choledocholithiasis were selected for laparoscopic

cholecystectomy (LC) and IOR-ERCP. Informed consent was obtained. A laparoscopic surgeon performed cholecystectomy and a gastroenterologist performed ERCP during the same anaesthesia.

Rendezvous ERCP was successfully completed in 22 of 25 patients. The Rendezvous procedure could not be accomplished in 3 patients due to difficulty passing the guide wire from the cystic duct to the duodenum. One patient had a tortuous cystic duct, another had abnormal connection of the cystic duct to the right hepatic duct and the third had malignancy of the gallbladder occluding the connection with the common hepatic duct (CHD). All three underwent successful retrograde canulation of the common bile duct (CBD) during the same anaesthesia.

The 22 successful rendezvous ERCP procedures were compared with 22 control patients with cholelithiasis and choledocholithiasis, who underwent ERCP and LC separately. The mean (cumulative) operating theatre (OT) time for Rendezvous ERCP was 2.34 hrs. vs 3.15 hrs. for separate procedures. The mean cumulative procedure-related hospital stay for IOR-ERCP was 2.77 days vs 7.50 days for traditional LC and ERCP. There was no case of post ERCP pancreatitis (PEP) or other complications in the study group. In the control group 4.5 % patients had pancreatitis (mild), 4.5% had a minor GI bleed and 4.5% had basal atelectasis with transient respiratory failure.

Rendezvous ERCP appears effective and safe; it helps decrease OT time, hospital stay, and it may decrease the cost of treatment. Challenges associated with this approach are that the procedure requires expertise; a surgeon and gastroenterologist should be available at the same time; crowding in the OT; multiple instruments in the field of fluoroscopy causes deterioration in quality of imaging; air insuffla-

tion during ERCP causes small bowel distension which inconveniences the surgeon, and that ERCP must be performed in a supine position.

INTRODUCTION

Approximately 15% of patients who have laparoscopic cholecystectomy also have CBD calculi [1,2], and according to Collins et al. (2004), two thirds of these patients need some intervention to remove them.[3] Current practice is to perform ERCP followed by laparoscopic cholecystectomy or vice versa, depending on local expertise and protocols.[4] With this approach, patients must undergo anaesthesia/sedation on two occasions. There is a 40-70% chance of false negative pre-operative ERCP [5], as a CBD stone will pass spontaneously in 50% cases before the procedure.[8] In 12.9 % of cases, new CBD stones may be discovered after laparoscopic cholecystectomy.[6] If ERCP is performed post-laparoscopic cholecystectomy, there is a 5% risk of failed cannulation, leading to a second surgery.[7]

The above pitfalls can be avoided using the Intra-operative Rendezvous ERCP technique. This procedure also reduces the risk of inadvertent cannulation of the pancreatic duct and risk of post ERCP pancreatitis.[8] In case ERCP fails, the option of CBD exploration is available during the same surgical session.

METHOD

In our case series, 25 patients (13 female and 12 males) with CBD and GB stones, with or without cholecystitis, pancreatitis or cholangitis, were selected for intra-operative ERCP. The rendezvous technique was followed as previously described [9]. Laparoscopic surgery was performed by one of three laparoscopic surgeons- AK, RT or MS. ERCP was performed by APU in all cases. A laparoscopic surgeon performed the intra-operative cholangiogram after isolating and opening the cystic duct. Once CBD calculi were confirmed, the surgeon passed a guidewire via the cystic duct into the CBD and duodenum. The Endoscopist then retrieved this wire through the instrument channel of the side-viewing duodenoscope using a snare, and used this guidewire to perform further instrumentation. Wire-guided biliary sphincterotomy was performed with or without balloon ampuloplasty. CBD stones were removed using stone retrieval balloons. CBD stenting was performed if stone extraction was considered incomplete, or if requested by the operating surgeon on a case-by-case basis. An occlusion cholangiogram was performed in all cases, to make sure of adequate clearance of the biliary tree. In cases where the guide wire could not be passed into the duodenum through the cystic duct (3 cases), we proceeded to perform ERCP in a supine posture in the same surgical session using standard cannulation techniques. This was successful in all 3 cases.

These outcomes were compared with 22 similar historical controls who underwent LC and ERCP separately. The following outcomes were analyzed:

- Procedure-related hospital stay- the number of days patients had to stay in hospital specifically to undergo the procedure(s).
- Procedure-related cumulative OT time- the total time spent by the patient under anaesthesia for LC and ERCP separately versus IOR-ERCP. Time under anaesthesia was retrieved from the OT procedure log.
- Procedure-related complications such as pancreatitis, bleeding, infection, perforation etc.

RESULT

Of a total of 25 patients, 12 were male and 13 were female. Ten cases had CBD calculus with acute calculus cholecystitis; 5 had biliary acute pancreatitis and evidence of retained CBD calculus after recovery, along with cholelithiasis; 9 patients had CBD calculus with cholelithiasis without cholecystitis; 1 case had gallbladder and CBD sludge, with microliths causing recurrent biliary colic (Table 1).

Rendezvous ERCP was successful in 22 patients (88%), 11 male and 11 female. The guide wire did not pass into the distal CBD in 3 (1 male and 2 female) patients (12%), who then had retrograde cannulation of the CBD during the same surgery, followed by completion of lap cholecystectomy. Of these three, one patient had a corkscrew cystic duct and guidewire coiled up in the duct/neck of the GB repeatedly. One patient had an anatomical variation wherein the cystic duct was inserted into the right hepatic duct (figure 2); the guide wire could not be negotiated into the CBD. One patient was found to have a Carcinoma gall bladder that was not diagnosed on prior imaging, this patient also had carcinoma of the stomach (figure 1). The cystic duct was completely blocked, and the guide wire could not be negotiated.

The outcomes of the study population are shown in Table 1. Post-operative outcomes of successful rendezvous ERCP were compared with similar numbers of historical controls. Hospital records of the last consecutive 22 patients (11 female; 11 male) having CBD stones and cholelithiasis who underwent ERCP followed by laparoscopic cholecystectomy were retrieved. Comparative outcomes of the study group and the control group are shown in Table 2.

The average (procedure-related) hospital stay in the

study group was 2.77 days, ranging from 2-5 days, compared to 7.5 days with a range of 5-12 days in the control group. The average (procedure-related, cumulative) OT time for the rendezvous procedure was - 2.34 hrs (range 2.0-3.2hrs). The cumulative OT time for traditionally managed patients was 3.15 hrs with a range of 1.55-5.15hrs. There were no cases of post ERCP pancreatitis or other complications in the study group. Three patients had minor complications in the control group. One (4.5%) had mild pancreatitis; One (4.5%) had minor post ERCP GI bleed, and one (4.5%) had basal atelectasis with transient respiratory failure. There was no mortality in either group.

Table 1: Patients data and outcomes for LC + IOR-ERCP.

Patient Age (yrs) and sex	Diagnosis	Procedure	Length of hospital stay (total days)	Post-ERCP pancreatitis and other complications.	Duration of procedure (hours)
44 female	CBD stone, acute cholecystitis, biliary pancreatitis	IOR-ERCP	3	Nil	2.45
40 female	CBD stone, acute cholecystitis, biliary pancreatitis	IOR-ERCP	2	Nil	2.15
30 female	CBD stone, acute cholecystitis, biliary pancreatitis	IOR-ERCP	2	Nil	2.30
42 female	CBD stone, acute cholecystitis, biliary pancreatitis	IOR-ERCP	2	Nil	2.30
35 female	CBD stone, acute cholecystitis	IOR-ERCP	2	Nil	2.15
35 female	CBD stone, acute cholecystitis with cholangitis	Failed due to malignancy of GB. ERCP done.	4	Nil	4.15
32 female	Gallbladder and CBD sludge and microliths. With pregnancy	IOR-ERCP	2	Nil.	2
29 female	Gallbladder and CBD calculus without cholecystitis and cholangitis	IOR-ERCP	2	Sludge blocking of CBD stent.	2.10
37 Male	CBD stone With acute cholecystitis	Failed due to tortuous cystic duct. ERCP done.	5	Nil	2
45 female	CBD stone With acute cholecystitis and jaundice	Failed due to anatomical variability, cystic duct connected with right hepatic duct. ERCP performed.	4	Nil	3.25
48 Male	CBD stone without Cholecystitis or cholangitis	IOR-ERCP	2	Nil	3
43 Male	CBD stone, acute cholecystitis, biliary pancreatitis	IOR-ERCP	3	Nil	2.30
39 female	GB and CBD stone and acute cholecystitis	IOR-ERCP	3	Nil	3
49 male	GB and CBD stone and acute cholecystitis	IOR-ERCP	5	Nil	3.15
39 male	GB and CBD stone and acute cholecystitis	IOR-ERCP	5	Nil	3.20
26 male	GB and CBD stone and acute cholecystitis	IOR-ERCP	4	Nil	2.0
35 female	GB and CBD stone	IOR-ERCP	3	Nil	2.2
40 female	GB and CBD stone	IOR-ERCP	3	Nil	2.3
46 male	GB and CBD stone	IOR-ERCP	2	Nil	2.1
45 male	GB and CBD stone	IOR-ERCP	4	Nil	2.0
38 male	GB and CBD stone	IOR-ERCP	2	Nil	2.2
42 male	GB and CBD stone	IOR-ERCP	2	Nil	2.0
39 male	GB and CBD stone	IOR-ERCP	3	Nil	2.2
37 male	GB and CBD stone	IOR-ERCP	2	Nil	2.5

44 female	GB and CBD stone	IOR-ERCP	2	Nil	2.0

DISCUSSION

There are several potential advantages to performing rendezvous ERCP during lap-cholecystectomy, such as: single anaesthesia, decreased cumulative OT time, decreased hospital stay and potentially a reduced risk of pest-ERCP pancreatitis. All of these may translate to reduced costs for the patient.

The average hospital stay in our series was 2.77 days. Most procedures were performed for patients who presented with acute cholecystitis or biliary acute pancreatitis. Procedure-related hospital stay was calculated by specifically considering the number of days patients had to stay in hospital for undergoing ERCP or surgery, after discounting the time spent in recovery from pancreatitis or acute cholecystitis.

The duration of hospital stay for the control group was 7.5 days. This appears to be unusually long. The reasons for this may be administrative in nature; Administrative issues such as insurance approvals, scheduling by the OT/surgeon etc. consume time and need to be factored in. Since joint procedures require a single approval from the payer, time is saved. This emerges as a distinct advantage of the combined approach wherein time spent in hospital due to administrative issues is also shortened.

The most alluring potential advantage of the joint approach is, however, a decrease in post-ERCP pancreatitis (PEP), since accidental cannulation of the pancreatic duct can be avoided. Pancreatitis may still occur by virtue of passage of the guidewire through the ampulla, involuntary pushing stones through the papilla, reflux of the biliary contrast into the pancreatic duct etc. Nevertheless, most studies have shown a trend toward reduction in rates of PEP. We did not have any cases of pancreatitis in our series.

We observed one patient who was pregnant with GB and CBD stones. IOR-ERCP was performed without fluoroscopy. This was only possible because of the certainty of biliary access that is offered by the joint approach. This came across as an advantage in our brief experience.

Theoretically, it may be redundant to have an MRCP before LC + IOR-ERCP, since an intra-operative cholangiogram will be performed in all cases. We, however, still prefer to perform MRCP prior to surgery as it can give valuable information about biliary anatomy. One of our patients had a cystic duct inserted in the RHD and the guide wire could not be negotiated distally. The rendezvous procedure can be avoided in such cases.

There are several challenges associated with a joint approach. Firstly, the operating surgeon and endoscopist must be available at the same time. This can prove challenging in busy hospitals.

There is also some crowding of equipment in the OT. It takes several sessions to streamline the positioning of surgical equipment and endoscopy tower before each team can position themselves comfortably. Multiple instruments interfere with the field of procedure and imaging (Figure 3); this causes deterioration in the quality of fluoroscopy due to interference from laparoscopic ports. ERCP must be performed in a supine posture (not all endoscopists are comfortable with this).

Table 2: Comparison of duration of procedures and hospital stay between traditional LC and ERCP vs Intra-operative Rendezvous ERCP.

	LC n=22 M-11, F-11	Traditional ECRP n=22	Cumulative OT time (LC+ERCP)	Rendezvous ERCP- All cases n=25	Rendezvous ERCP- successful cases. n=22 M-11, F-11
Duration of procedure (hrs): Mean (range)	1.85 (1-4.20)	1.30 (0.30-2.00)	3.15 (1.55-5.15)	2.44 (2.0-4.15)	2.34 (2.0-3.20)
Duration of hospital stay (days): Mean (range)	3.41 (2-6)	4.08 (1-9)	7.5 (5-12)	2.92 (2-5)	2.77 (2-5)
complications		1 case of post-sphincterotomy GI bleed. 1 case of post-ERCP pancreatitis. 1 case of atelectasis with respiratory failure.		Nil	Nil

Figure 1: Endoscopic image of gastric carcinoma, found during rendezvous ERCP.

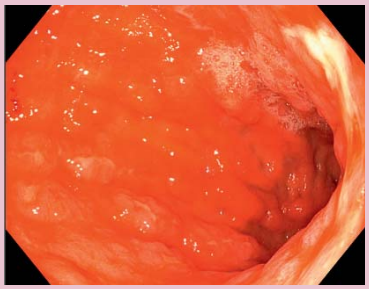


Figure 2: Fluoroscopic image of rendezvous ERCP showing abnormal cystic duct connection with right hepatic duct.

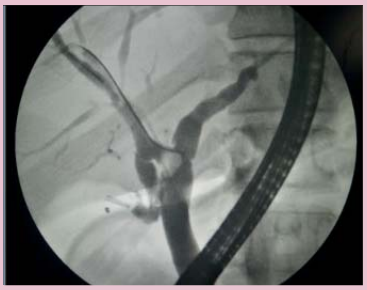
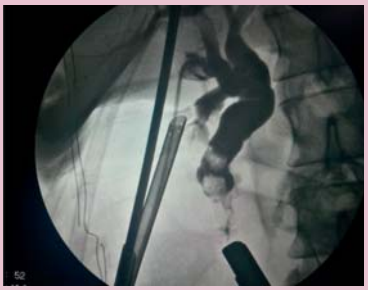


Figure 3: Fluoroscopic image of rendezvous ERCP with multiple instruments in the field of procedure.



Gas insufflation in the small bowel during ERCP can also cause technical difficulty for the operating surgeon. In our experience, various operating teams adapted readily to these challenges and the learning curve was very brief. Since all ERCPs in our hospital are performed under GA and in a supine posture, this issue was not an obstacle in our experience. However, practice of ERCP varies across the world.

Since our endoscopy suite does not have lead-lined walls, we perform all our ERCPs in the OT under GA. This has not changed in this study. We do not have data to compare time spent on the actual performance of ERCP as this is not routinely recorded. We assume that time spent in attempting selective bile duct canulation would be significantly shortened using the combined approach.

As previously mentioned, we faced failure of antegrade CBD access by guide wire in three cases due to various technical reasons- one due to a "corkscrew" cystic duct, one due to variant anatomy of the CBD's abnormal connection with the right hepatic duct and one due to previously undiagnosed gallbladder malignancy. Careful analysis of MRCP images in retrospect suggested that we could have avoided the Rendezvous procedure in two of these patients from the outset. This also highlights the fact that the Endoscopy team must be prepared to perform ERCP using retrograde canulation of the CBD in a supine posture, should the need arise.

CONCLUSION

Rendezvous ERCP during laparoscopic cholecystectomy is a promising technique that is technically feasible in most setups. It is an efficient and safe treatment for patients with choledocholithiasis and cholelithiasis. It helps to reduce overall length of hospital stay as well as time spent under anaesthesia [10]. There may be additional advantages such as reduction in rates of post-ERCP pancreatitis that need to be confirmed in larger studies.

LIST OF ABBREVIATIONS

- ERCP endoscopic retrograde cholangiopancreatography
- MRCP magnetic resonance cholangiopancreatography
- CBD common bile duct
- CHD common hepatic duct
- LC laparoscopic cholecystectomy
- GB gall bladder
- MPD major pancreatic duct
- GA general Anaesthesia
- GE gastro-oesophageal
- OT operation theatre
- OGD oesophago-gastro-duodenoscopy
- RHD right hepatic duct

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A luminous journey into cellular biology

The Song of the Cell is the vivid, thrilling and suspenseful story of the fundamental unit of life. It describes how scientists discovered cells, began to understand them, and are now using that knowledge to create new humans.

The Song of the Cell: An Exploration of Medicine and the New Human

Written By:
Siddhartha Mukherjee

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Mukherjee, a physician, professor of medicine, and Pulitzer Prize–winning author *(The Emperor of All Maladies)*, has a knack for explaining difficult ideas in terms that are both straightforward and interesting. In his latest, he punctuates his scientific explanations with touching, illustrative stories of people coping with cell-based illnesses, tracking how the knowledge gleaned from those cases contributed to further scientific advancement. In the early chapters, the author traces the discovery of cells as the building blocks of animal and plant life, with the invention of the microscope making analysis possible.

With this development, researchers could better understand the roles of cells in human physiology, including the illnesses that rogue cells could cause. In the middle section, Mukherjee investigates how scientists then moved on to study the processes through which cells become specialized by function and how some turn cancerous. The identification of the phases of cell division and the discovery of DNA were crucial breakthroughs, opening the way for a new generation of treatments. Mukherjee occasionally digresses from the historical story to provide vivid portraits of key researchers, with recollections about his own work. The final section of the book deals with emerging areas of research such as cell manipulation and gene editing as well as new technologies like transplantation. It's all unquestionably exciting, but the author is careful to acknowledge the knotty ethical considerations. Treating embryos for cellular abnormalities makes medical sense, but the idea of altered human beings have worrying implications. Mukherjee also emphasizes that there is still a great deal we do not know about cells, especially the interactions between types. Understanding the mechanics is one thing, he notes; hearing "the song of the cell" is something else. This poignant idea serves as a suitable coda for a fascinating story related with clarity and common sense.

The Song of the Cell is the vivid, thrilling and suspenseful story of the fundamental unit of life. It describes how scientists discovered cells, began to understand them, and are now using that knowledge to create new humans. Both panoramic and intimate, it is Siddhartha Mukherjee's most spectacular book yet.

In the late 1600s, a distinguished English polymath, Robert Hooke, and an eccentric Dutch cloth-merchant, Antonie van Leeuwenhoek, look down their hand-made microscopes. What they see introduces a radical concept that alters both biology and medicine forever. It is the fact that complex living organisms are assemblages of tiny, self-contained, self-regulating units. Our organs, our physiology, our selves, are built from these compartments.

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Rich with stories of scientists, doctors, and the patients whose lives may be saved by their work,

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Aster Volunteers was founded with the aim of serving as a catalyst for social impact action and to function as a platform for all those who wish to contribute to its humanitarian efforts. Through our efforts, **9086+** volunteers have impacted **1 Million+** lives and counting.

*dated as on 31st May 2019

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