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Letter to the Editor

First case of monkeypox virus, SARS-CoV-2 and HIV co-infection

Dear Editor,

In this journal E. Orviz and colleagues recently described the clinical presentation of the first monkeypox patients in Spain, [1] highlighting the frequent co-presence of sexually transmitted infections (STI). To date, no reports of co-infection with monkeypox virus and SARS-CoV-2 have been published. Therefore, in this study we present the clinical features and diagnostic procedure of the first documented case of co-infection with monkeypox virus, SARS-CoV-2 and HIV-1.

Since January 2022, more than 16,000 people in over 74 countries have been affected by monkeypox, prompting the World Health Organization to declare this outbreak a public health emergency of international concern [2,3]. Human-to-human transmission occurs through close contact with infectious material from skin lesions, fomites, seminal fluids and oropharyngeal secretions [1,4–6]. The majority of cases were registered in gay or bisexual men often suffering from other STI [1,5,6]. At the same time, SARS-CoV-2 is still a major cause of morbidity and mortality globally. COVID-19 shares with monkeypox both the transmission by air droplets and the symptoms of fever, lymphadenopathy, headache, sore throat and fatigue [5]. As these pathogens continue to spread, individuals can be simultaneously infected with monkeypox virus, SARS-CoV-2 and STI, making it difficult for physicians to perform the correct diagnosis, also considering that not all patients with monkeypox develop skin lesions and that COVID-19 may rarely present with rash and vesicles [6,7].

Our patient, an Italian 36-year-old male spent 5 days in Spain from 16 to 20 June 2022 (Fig. 1). Nine days after, he developed fever (up to 39°C), accompanied by sore throat, fatigue, headache and right inguinal lymphadenomegaly. On 2 July he resulted positive for SARS-CoV-2. On the afternoon of the same day a rash started to develop on his left arm. The following day small, painful vesicles surrounded by an erythematous halo appeared on the torso, lower limbs, face and glutes. On 5 July, due to a progressive and uninterrupted spread of vesicles that began to evolve into umbilicated pustules, he went to the emergency department of the Policlinico “G. Rodolico - San Marco” University Hospital in Catania, Italy, and was subsequently transferred to the Infectious Diseases Unit.

On admission, the patient reported being treated for syphilis in 2019. In September 2021, he performed an HIV test with a negative result. He suffered from bipolar disorder, for which he regularly took carbamazepine 200 mg daily. He was vaccinated for SARS-CoV-2 with two doses of Pfizer’s BNT162b2 mRNA vaccine (the last in December 2021) and had already contracted COVID-19 in January 2022. He also reported of having condomless intercourse with men during his stay in Spain. Fever (37.5°C), pharyngodynia, fatigue, headache were still present. On physical examination his body was dotted, including the palm of the right hand and the perianal region, with skin lesions in various stages of progression, ranging from small vesicles (Fig. 2, Panel A) to reddened haloed pustules (Fig. 2, Panel B and Panel C) and umbilicated plaques (Fig. 2, Panel D). The oral mucosa was normal, except for bilateral tonsillar hypertrophy. A modest hepatosplenomegaly and an enlarged (2 cm), hypomobile and painful lymph node in the right inguinal region were found. Laboratory tests showed elevated C-reactive protein (69 mg/L, normal values 0.0 - 5.0 mg/L), fibrinogen (713 mg/dL, normal values 170 - 400 mg/dL) and prothrombin time (1.21, normal values 0.8 - 1.2). Chest X-ray revealed a parenchymal hypodiaphany in the right parailary region.

On the second day of admission (July 6, 2022), given the high suspicion of monkeypox supported by suggestive skin lesions and a recent trip to Spain, [1] swabs of pustule exudate and nasopharynx secretions were sent to the Regional Reference Laboratory hosted at the University Hospital “P. Giaccone” of Palermo (Italy) for monkeypox *orthopoxvirus* detection and SARS-CoV-2 sequencing. To this purpose, monkeypox virus DNA was extracted using Quick-DNA™ Miniprep Plus extraction kit (Zymo Research), whereas SARS-CoV-2 RNA was extracted using QIAamp Viral RNA extraction kit (QIAGEN). Eluted DNA/RNA was stored immediately at -80°C until further use or analysed by means of rt-PCR assays. Three different singleplex rt-PCR assays targeting the TNF receptor gene of monkeypox were used: a monkeypox generic assay and two further rt-PCR assays specifically designed to differentiate monkeypox Congo Basin and West African strains [8]. All rt-PCR assays were performed with a QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems, Carlsbad, USA) and a test was considered positive when its cycle threshold value was <40. SARS-CoV-2 genome was generated by next-generation sequencing on an Ion GeneStudio™ S5 System (Applied Biosystems, Carlsbad, USA) using the Ion Ampliseq™ SARS-CoV-2 Research Panel and virus lineage was designated using the Pangolin dynamic nomenclature system [9,10]. SARS-CoV-2 genome included in the study was submitted to the Global Initiative on Sharing All Influenza Data (GISAID) repository (https://www.gisaid.org).

The specimens were confirmed positive to monkeypox virus and SARS-CoV-2. The first belonged to the West African clade, the variant responsible for the Spanish outbreak, [1] while SARS-CoV-2 genome classified by Pangolin as lineage BA.5.1 (GISAID Accession ID: EPI_ISL_13876417). Serology tests for viral hepatitis, herpes simplex, gonorrhoea, chlamydia and lymphogranuloma venereum were negative. However, HIV-1 resulted positive with a viral load of 234,000 copies/mL. The $CD4^+$ lymphocyte count was unaltered with 812 cells/μL (normal values within 410-1590 cells/μL).

The third day almost all skin lesions began to turn to crusts. Sotrovimab 500 mg was infused intravenously. On day 5 (July 9, 2022), almost all constitutional symptoms were resolved and previously altered laboratory test values normalized. On day 6 (July

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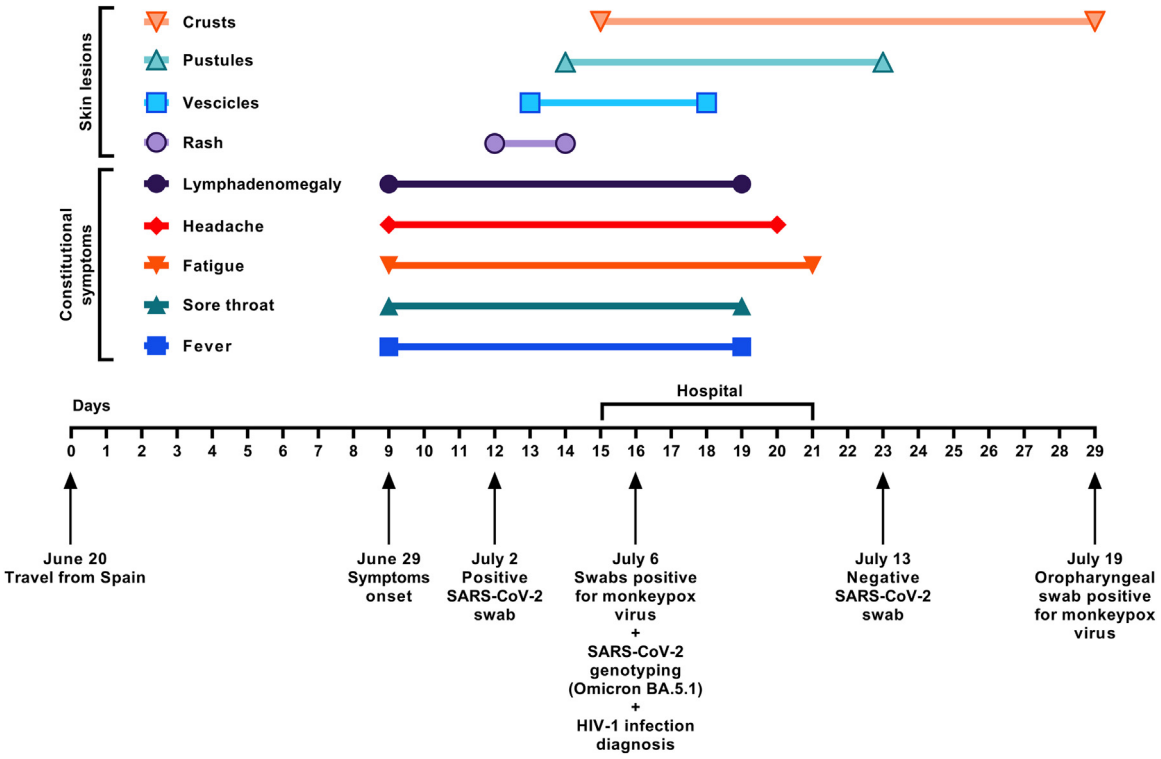

Fig. 1. Symptoms and skin lesions, from June 20 to July 19, 2022.

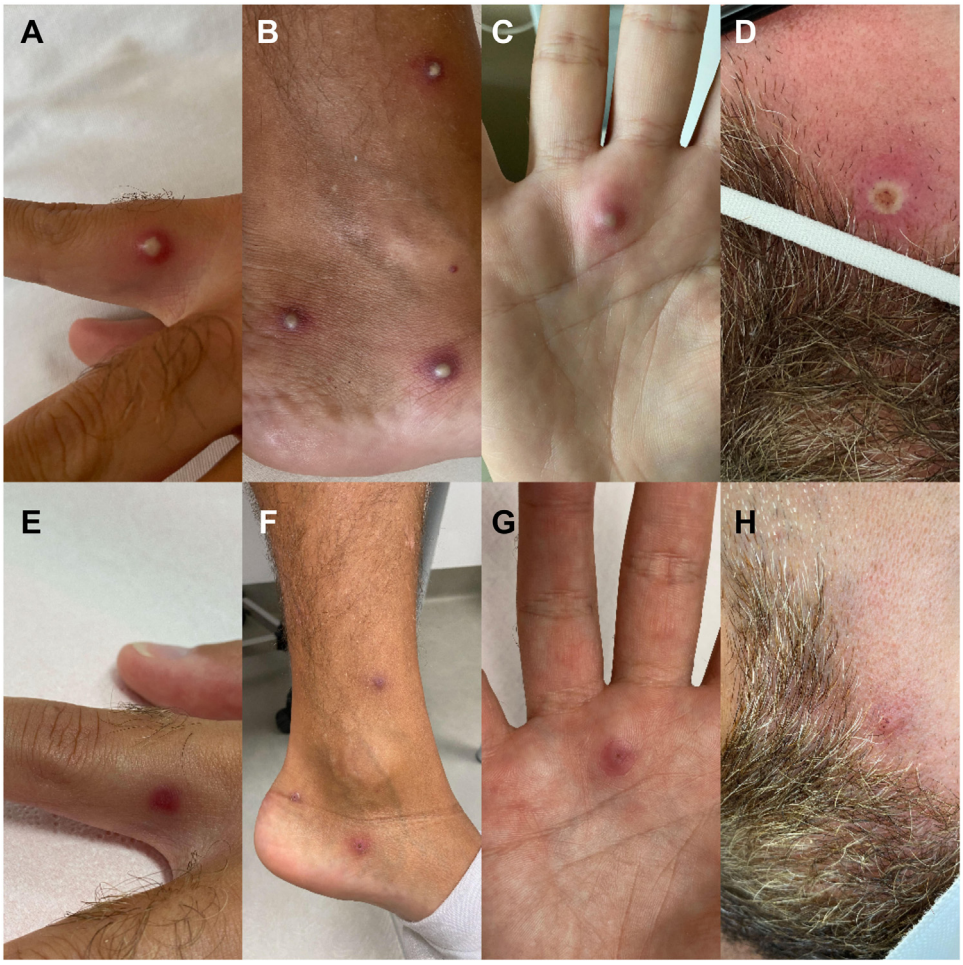

Fig. 2. Monkeypox skin lesions: small vesicles (Panel A), reddened haloed pustules (Panel B and Panel C) and umbilicated plaques (Panel D). After 16 days, the lesions had almost healed, leaving a small scar (Panels E to H).

11, 2022), nasopharyngeal swabs for SARS-CoV-2 and monkeypox virus were still positive, despite the absence of new skin lesions. Since symptoms had resolved, the patient was discharged to home isolation. On 19 July 2022 he returned to our institute to underwent a new oropharyngeal swab for monkeypox virus, which was still positive. The crusts had healed almost completely, leaving a small scar (Fig. 2, Panels E to H). A triple combination of dolutegravir, abacavir and lamivudine was initiated for HIV treatment.

This case highlights how monkeypox and COVID-19 symptoms may overlap, and corroborates how in case of co-infection, anamnestic collection and sexual habits are crucial to perform the correct diagnosis. SARS-CoV-2 BA.4 and BA.5 subvariants are currently responsible for more than 1 million COVID-19 cases per day worldwide. Hence, clinicians should be aware of the possibility of SARS-CoV-2 and monkeypox virus co-infection, particularly in subjects with a recent history of travel to monkeypox-outbreak areas. If monkeypox is suspected, an oropharyngeal swab should be performed even in the absence of cutaneous manifestations as the skin may be spared, but the oral or rectal mucosa may be involved [4–6].

Our case emphasises that sexual intercourse could be the predominant way of transmission. Therefore, complete STI screening is recommended after a diagnosis of monkeypox. In fact, our patient tested positive for HIV-1 and, given his preserved $CD4^+$ lymphocyte count, we could assume that the infection was relatively recent. To note, the monkeypox oropharyngeal swab was still positive after 20 days, suggesting that these individuals may still be contagious for several days after clinical remission. Consequently, physicians should encourage appropriate precautions. As this is the only reported case of monkeypox virus, SARS-CoV-2 and HIV co-infection, there is still not enough evidence supporting that this combination may aggravate patient's condition. Given the current SARS-CoV-2 pandemic and the daily increase of monkeypox cases, healthcare systems must be aware of this eventuality, promoting appropriate diagnostic tests in high-risk subjects, which are essential to containment as there is no widely available treatment or prophylaxis.

Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Contributorship statement

All authors contributed equally to this work.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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