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Monkeypox outbreak in Spain: clinical and epidemiological findings in a prospective cross-sectional study of 185 cases.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.21790

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Key words: Monkeypox; epidemiology;

Word count: 2604

Author contributions: Dr. Catala, Dr. Riera, Dr. Clavo, Dr. Martin and Dr. Fernández-Gonzalez contributed equally to this article.

Funding/Support:
This study was supported by *Fundación Piel Sana Academia Española de Dermatología y Venereología* with the participation of *the Grupo Español de Investigación en ETS y SIDA de la AEDV (Academia Española de Dermatología y Venereología)*. This paper was prepared or accomplished by the authors in their

personal capacity. The opinions expressed in this article are the author's own and do not necessarily reflect the view of the *Academia Española de Dermatología y Venereología*.

Financial disclosure of the authors:
None of the authors has a financial conflict of interest to disclose in relation to this topic.

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Acknowledgement:
We are especially grateful to the generous patients that consented to have their pictures published to improve diagnosis and outbreak control. We thank Marina de Vega (as study monitor strictly checking for compliance with research ethics) and the following clinicians: Mireia Segui-Olmedilla, Mar Llamas, David García, Nicolás De Loredo, Guillermo F. Del Carlo, Ana González, Estela Solbes, Gerald Selda-Enríquez, Ana Melián-Olivera, Patricia Burgos-Blasco, María González-Ramos, Emilio Garcia-Mouronte, Javier Pérez-Bootello, Carlos Azcarraga-Llobet, Luis Alfonso Pérez-González, Jorge Naharro-Rodriguez, Maria Jesús Vivancos-Gallego, María Jesús Pérez-Elías, Juan-Carlos Galán, Nerea Manzanares, Cristina Barrabés Torrella, Helena Escola, Mar Llamas, Santiago Moreno, Pedro Jaén-Olasolo. This work is part of the PhD degree of Josep Riera, in the Department of Medicine, Dermatology area, Universidad de Barcelona.

Supplementary material

1. Photographic atlas
2. Supplementary statistical analysis
3. Translated questionnaire

Abstract

Background: Since May 2022, a new outbreak of monkeypox has been reported in several countries, including Spain. The clinical and epidemiological characteristics of the cases in this outbreak may differ form earlier reports.

Methods: We conducted a prospective cross-sectional study in multiple medical facilities in Spain to describe the cases of monkeypox in the 2022 outbreak.

Results: In total, 185 patients were included. Most cases started with primarily localised homogeneous papules, not pustules, in the probable area of inoculation, whichcould be cutaneous or mucous, including single lesions. Generalised small pustules appeared later in some of them. Heterogeneous lesions occurred during this generalised phase. All patients had systemic symptoms. Less common lesions included mucosal ulcers (including pharyngeal ulcers and proctitis) and monkeypox whitlows. Four patients were hospitalised, none died. Smallpox vaccination and well-controlled HIV disease were not associated with markers of severity. Contact during sex is the most likely mechanism of transmission. In this outbreak, cases have been described in males having sex with males and are strongly associated with high-risk sexual behaviours. Seventy-six percent of the patients had other sexually transmitted diseases upon screening.

Conclusions: The clinical findings in this outbreak differ from previous findings and highly suggest contact transmission and initiation at the entry site. The characterisation of the epidemiology of this outbreak has implications for control.

What is already known about this topic?

Monkeypox eruption is described as consisting of pustules. The role of HIV and previous smallpox vaccination in prognosis are unknown. Transmission route was initially described as respiratory droplets and later suggested to be via sexual contact.

What does this study add?

Initial lesions at the probable inoculation area were homogeneous and papular (pseudopustules) Generalised small pustules appeared later in some of them. Heterogeneous lesions occurred during this generalized phase. All patients had systemic symptoms. Less common signs included mucosal ulcers (including pharyngeal ulcers and proctitis) and monkeypox whitlows. Well-controlled HIV and previous smallpox vaccination were not associated with severity. No patient died. Data support the hypothesis of transmission via contact during sex. Although this might change, the outbreak is currently limited mostly to males having sex with males with high-risk factors for sexually transmitted-diseases.

Monkeypox is a zoonotic disease caused by the monkeypox virus, which belongs to the Orthopoxvirus genus. This genus also comprises variola virus (the causative agent of smallpox), vaccinia virus, and cowpox virus.

Monkeypox disease was endemic in Africa, causing periodic outbreaks[1,2], but a change seems to have taken place from a predominantly animal-to-human transmission to a more common human-to-human transmission[3]. Outside Africa, the first cases were reported in 2003 in the United States, also likely to be due to animal-to-human transmission[3,4]. Since May 2022, an outbreak of monkeypox has been reported in countries across five WHO regions (the Americas, African, European, Eastern Mediterranean, and Western Pacific regions). As of 15 June 2022, a total of 2103 laboratory confirmed cases have been reported to the WHO, 497 in Spain[5,6].

The incubation period is 5 to 21 days[7] and patients with cutaneous lesions are considered infectious, but transmission might start with prodromic symptoms before the onset of cutaneous lesions[8,9]. The classically described clinical picture of monkeypox consisted in fever and lymphadenopathy, followed by a generalised rash. The skin eruption has been described as beginning on the face and then spreading to other parts of the body (legs, trunk, arms, palms, soles, genitalia, etc.). The evolution of the rash progresses through the following stages: maculopapular (lesions with a flat base), vesicular (small fluid filled blisters), pustular (pus-containing rash) and crust (dried blisters)[10].

Cases in this new outbreak have been described as atypical: with few lesions, sometimes localised to a single area, and with lesions appearing at various stages of development (asynchronous)[5,7]. Other orthopoxviruses (i.e., cowpox virus, camelpox virus, buffalopox virus) and parapoxviruses (i.e., orf virus, pseudocowpox virus, bovine

papular stomatitis virus) usually cause localized skin lesions in humans at the site of inoculation and this might be the situation in the current outbreak[7].

Human-to-human or secondary transmission was considered to mostly occur through respiratory droplets during direct and prolonged face-to-face contact; by direct contact with body fluids of an infected person, by contact of mucosa or non-intact skin with open rash lesions; or by contact with contaminated objects[7]. Sexual transmission was first suggested in the 2017 outbreak in Nigeria[11] , occurring in male and female patients, and is considered possible in the current outbreak[7], as it primarily affects men who self-identify as having sex with men (MSM) and have reported recent sex with new or multiple partners. More invasive routes of inoculation (i.e. mucocutaneous vs transdermal) have been linked to a more severe disease and shorter incubation period[12], and this might explain the clinical differences in this new outbreak.

Regarding factors for severity, in a small retrospective series of 34 patients in the USA, smallpox vaccination was not associated with disease severity or hospitalization[13]. The effect of HIV on the severity of monkeypox is unknown.

Our aims were to describe the clinical findings in the current outbreak in Spain, to explore the possibility of a localised form of the disease and whether it is linked to differences in incubation period or severity, to describe associated factors for severity, including the effect of previous smallpox vaccination and HIV, and to investigate the epidemiological characteristics of the current outbreak.

Methods

STUDY DESIGN AND INCLUSION CRITERIA

All dermatologists in Spain were invited to participate through a pre-existing network[14]

from 28 May to 14 July , 2022. Consecutive patients were prospectively included in the study if they had suggestive skin lesions. We only included in this publication those with demonstration of the presence of Orthopoxvirus or monkeypox virus DNA by polymerase chain reaction (PCR) testing, in agreement with the European Centre for Disease Control confirmed case definition at the time of protocol writing PCR testing was conducted for Orthopoxvirus in the first 3 or 4 days of the study, when inclusions were fewer, but was specific for monkeypoxvirus during the majority of the study.

DATA COLLECTION AND STATISTICAL ANALYSIS

Study data were collected using REDCap electronic data capture tools in a predefined questionnaire that remained unchanged during the study (Supplementary file). As the questionnaire was planned at the very beginning of the outbreak many uncertainties were present. During the data collection period, frequent contact between the first authors was planned to discuss new clinical findings, so that newest hypothesis could be checked in susequent patients. Authors in the centers collecting more patients were able to gather extra data as required to reinforce some hypothesis, including through telephonic contact with patients to improve the description of the evolution of lesions. Unless otherwise indicated, all quantitative data results from the analysis of the preplanned questionnaires.

The analysis consisted of a description of the data and distribution tests ($\chi 2$-test for qualitative variables and Mann-Whitney test for quantitative variables) and was done using Stata 17 (StataCorp, College Station, TX, USA).

For hypothesis testing, we defined the localized form as having ≤25 lesions and ≤3 affected zones. Generalised forms of the disease were defined as having four or more

affected zones.

Smallpox vaccination was compulsory in Spain until 1980. However, the previously high ratio of vaccines administered to newborns was lower than 60% since 1972, and quickly decreased since then[15]. BCG vaccination, which leaves a permanent scar, was more common than smallpox vaccination in the 60-70s, limiting the validity of a scar as a marker of smallpox vaccination[15]. For analyses we considered those born before 1972 as vaccinated for smallpox.

As the number of serious outcomes (hospitalization, death) was expected to be low, we used the number of lesions and extension as proxy markers for severity[13,16].

The study was approved by the Ethics Committee of Hospital Universitario Puerta de Hierro (17/05/22, CP01.22). All patients provided informed consent to include their data in the study. Images were only collected if the patient gave a specific consent.

Results

PATIENTS

One hundred eighty-five patients were included in the study, which composed 9% of those reported to the national surveillance system (which included 2034 cases on11 July)[17]. Fourteen patients were excluded due to lack of PCR confirmation of the diagnosis.

The characteristics of the population are described in table 1. All patients were male. Ten percent were born before 1972, and therefore highly likely to have received smallpox vaccination. Forty-two percent of the patients had HIV infection.

CLINICAL FEATURES

Most cases begin with lesions on the genitals, face, arms and hands and perianal area. These initial lesions, although similar in appearance to pustules, are not pustules but whitish solid papules, without a roof or liquid content. Over time their center becomes necrotic (Figure 1A). Single lesions were present in 11% of the patients. They can be very painful and might group in large plaques (Supplementary material). Circumscribed painful erythema and oedema can be a relevant feature, even with few overlying lesions.

Apart from these characteristic cutaneous lesions, there are additional details to be noted. Several patients had monkeypox whitlows (Figure 2). When present at mucosae these primary lesions may present as chancriform ulcers (Figure 3), causing oral ulcers (5%), proctitis (22%) or tonsillar ulcers (Figure 4) with surrounding oedema leading to dysphagia, and might affect the airway. The conjunctivae can also be affected (Supplementary material). Mucosal lesions can be the predominant lesions and, with whitlows and single lesions, were less likely to be recognized as monkeypox by physicians in our study. These primary papules or ulcers last for several weeks and can lead to atrophic scars.

Other lesions, which appeared later, are small vesicles with an erythematous halo leading to pustules (Figure 1B). They tend to be more scattered, asymptomatic or slightly itchy, and cured in a few days without scar. Lesions located on mucosal surfaces or which become superinfected can be more painful. Macular (morbilliform) eruptions are less common (6%) and appear later.

Overall, most patients had fewer than four affected areas (65%) and ≤25 lesions (89%). A single patient had associated erythema multiforme and some patients had bacterial superinfection.

All patients had systemic symptoms (100%), mostly lymphadenopathy (56%), fever (54%), myalgia (44%), asthenia (44%) and headache (32%). In most patients (98%) symptoms appeared the same day or a few days before the appearance of skin signs. Patients with generalized forms were more likely to have skin signs appearing days after experiencing symptoms (47% of patients with skin signs starting after symptoms vs 31%, p=0.04).

This description of a localised nodular-ulcerative form that can generalise with pustular lesions, is consistent with the quantitative analysis of questionnaire data. Generalised forms presented later after symptom onset (median 7 vs 6 days, U Mann-Whitney p<0.005, Supplementary tables) and were more likely to have lesions of different characteristics (74 vs 42%, Chi2 p<0.001) and papular (66 vs 40%, Chi-2 p<0.001), vesicular (41 vs 23%, Chi-2 p=0.012) and macular lesions (13 vs 3%, Fisher p=0.02). Incubation periods were similar for localised and generalised forms (median 6.5 vs 6, U Mann-Whitney, p=0.77, Supplementary tables).

Four patients (2%) required hospitalization (due to uncontrollable pain, severe dysphagia, conjunctival disease, and suspected colonic perforation due to traumatic anal sex after diagnosis), no patients died.

We attempted to describe the association of birthdate prior to 1972 (a possible protective factor for severity) or HIV infection (a possible risk factor) with other clinical findings, including number of lesions or affected areas, but found no relevant associations. Three of the four hospitalized patients were HIV-positive (Supplementary table).

EPIDEMIOLOGICAL FINDINGS

All cases of this outbreak were male andnearly all patients reported having sex with males (99%) and having multiple sexual partners during the previous weeks (Table 1). Other common characteristics were the use of drugs during sexual activity (34%), HIV positivity (42%) and diagnosis of a sexually transmitted disease in the previous year (54%). Although not included in the questionnaire, researchers reported that use of HIV pre-exposure prophylaxis was common in those negative for HIV (31/40 or 77%) in one center).

In those with a well-defined exposure, cases were mostly not imported, and the median incubation period was 6 days (p25:4-p75:9). An exposure could not be traced in 64% of patients. Other sexually transmitted diseases (STD) were detected with screening in 76% of the patients.

Discussion

Our main findings were the improved description of lesions. Our data strongly support physical contact as the infection route with localised initial papular lesions and a later eruption of vesiculopustular lesions. We suggest some clinical findings that are likely to remain undiagnosed and others that can lead to complications. The characterization of the epidemiology of this outbreak has implications for control.

Invariably, earlier descriptions defined monkeypox lesions as pustules (pus-filled lesions)[7,9,18,19]. This has important consequences for differential diagnosis, as there are many causes of pustules. However, participating dermatologists consistently described the primary lesions in the likely inoculation areas as papules that simulate pustules

(pseudo-pustules), in which it isimpossible to scrap the roof and obtain pus. Other poxviruses such as Orf, Milker's nodule or molluscum contagiosum lead to pseudo vesicular-pustular lesions (monkeypox whitlow is very similar to both Orf and Milker's nodule). Histologic descriptions of monkeypox pseudo-pustules confirm that the lesion is composed of keratinocytic debris and inflammation, and not liquid[20]. This information can be particularly useful for differential diagnosis of the initial lesions, as very few diseases produce pseudo-pustules. Varicella, as one of the most likely differential diagnoses, produces liquid filled lesions. Over time a secondary eruption of small pustules can take place in monkeypox. Other relevant clinical findings are the chancriform mucosal lesions, including proctitis and the possible initial lesions in the pharynx that can be difficult to diagnose, and can lead to dysphagia or potentially compromise the airway. Pain, dysphagia, and conjunctivitis were reasons for hospitalization, and this might be useful information to decide on the indications for antiviral therapy.

Dermatologists' descriptions and questionnaire data support the existence of initial papular localised lesions, probably occurring at the entry site, followed by distant pustular lesions. Previously described macular rashes were uncommon in our study and include in their differential diagnosis other STDs or drug eruptions. The rarity of patients with macular lesions in our sample might be real, or due to monkeypox not being suspected in patients with that type of lesions. All patients had systemic symptoms which usually appeared at the same time than the eruption, or a few days earlier. Although the design did not allow for a precise estimation of the risk for scars, participants indicated that in their experience, less than 20% of the patients had scars,

being more common in those with more inflammatory lesions.

Seventy-six percent of the cases had other STDs which were detected on screening. This implies that STD screening should be conducted in monkeypox patients and shows that even if another STD can be diagnosed, monkeypox should not be excluded. Such a high rate of coinfections raises the hypothesis of other STD being a facilitator for monkeypox infection.

Regarding risk factors for severity, we did not find a difference in extension or number of lesions between smallpox vaccinated or unvaccinated patients. However, this might not be an accurate measure of the effect of the vaccine in Monkeypox for multiple reasons. I this study the numbers of those born before 1972 are small. This date is only a proxy for the chances of receiving vaccination and use of this date does not allow to separate the effect of vaccination from age; the immunity might wane over time. HIV positivity was not associated with measures of symptom severity, but the HIV-positive population in the study showed very good HIV control, and our findings might not apply to patients with an uncontrolled HIV disease. These comparisons also have limitations due to the limited follow-up and the absence of serious outcomes in the sample. Furthermore, the proxy measures of severity were broadly categorised and the power to detect subtle differences in severity was low.

Several facts support contact during sex as the mechanism of transmission. Different lesions, probably primary, were centered in most patients in areas of close contact during sexual intercourse, and the outbreak remained limited to MSM, although this might change over time. If the viral infection were through airborne particles; the

outbreak would be more likely to affect a more heterogeneous population.

The current outbreak is affecting males having sex with males with multiple sexual partners and other risk behaviours for STDs. This might change over time (probably spreading to populations with higher risk of severity such as children or pregnant women) but the currently affected population offers relevant information for the outbreak control and might be useful to focus vaccination strategies. It is unlikely that these epidemiological findings can be due to differences in healthcare seeking or patient selection due to the type of clinics involved in the study, as the data in the current study come from varied settings including STD clinics, general consultations and emergency rooms. Although we do not have a comparison group, the proportions of high-risk sexual behaviors in these patients appear to be different than those in a general population.

As cutaneous lesions of monkeypox are noticeable, the fact that many patients do not report a contact with someone affected might mean that there is an asymptomatic infectious period, or infection through fomites. An alternative explanation could be that having sex without seeing partner's genitals and skin (due to low light or altered consciousness in chemsex) could be a risk factor for this disease. Prevalent viruses transmitted by contact such as genital warts or molluscum can be transmitted with hardly noticeable lesions. The visibility of monkeypox lesions could provide an opportunity for improved control if a policy to "make sure to see your partner skin before having sex" were promoted.

Advantages of the present study are that the sample is large and likely to be representative of cases in Spain, as it includes a relevant proportion of all cases, which

have been seen at diverse levels of the health system (emergency rooms, STD clinics and dermatology consultations) decreasing the risk of selection bias. The study is also likely to be exhaustive, as given the sample size, undetected events have an upper 95% confidence interval of prevalence of 1.6%. The study was prospective and used predefined variables to improve the validity of results. The main limitation is the brief period of follow-up, which makes the results on prognosis and sequelae less accurate. However, this limitation was reduced by considering the information from follow-up phone calls. Another possible limitation is that patients were included in the study if monkeypox was suspected. This might have excluded less symptomatic forms of the disease, biasing the results. Other questions that were not answered in this study include the precise prevalence of scars in those having monkeypox, which can have profound implications in terms of stigmatization, or an improved description of prognosis.

Conclusion

The current monkeypox outbreak seems to have different clinical characteristics than previously seen, probably being transmitted by contact, with papules starting at the cutaneous or mucous portal of entry and a later dissemination of pustules. None of the cases in the present study were life-threatening. The possibility of airway implication with pharyngeal oedema seems to be the highest risk scenario.

In the current outbreak all cases were men having sex with men with high-risk sexual behaviour. Co-infection with other STIs was frequent in patients diagnosed with monkeypox. Although it is likely to spread, the current outbreak is limited to a very specific population, and with due care to avoid stigmatization, all efforts of control

(information, vaccination) should be primarily addressed to this group, with the help of LGBT stakeholders, to protect them and offer an opportunity to control the outbreak.

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Figure legends

Figure 1. A) Initial papular lesion (pseudopustule). B) Later appearing pustule

Figure 2. Monkeypox whitlow

Figure 3. Chancriform ulcer

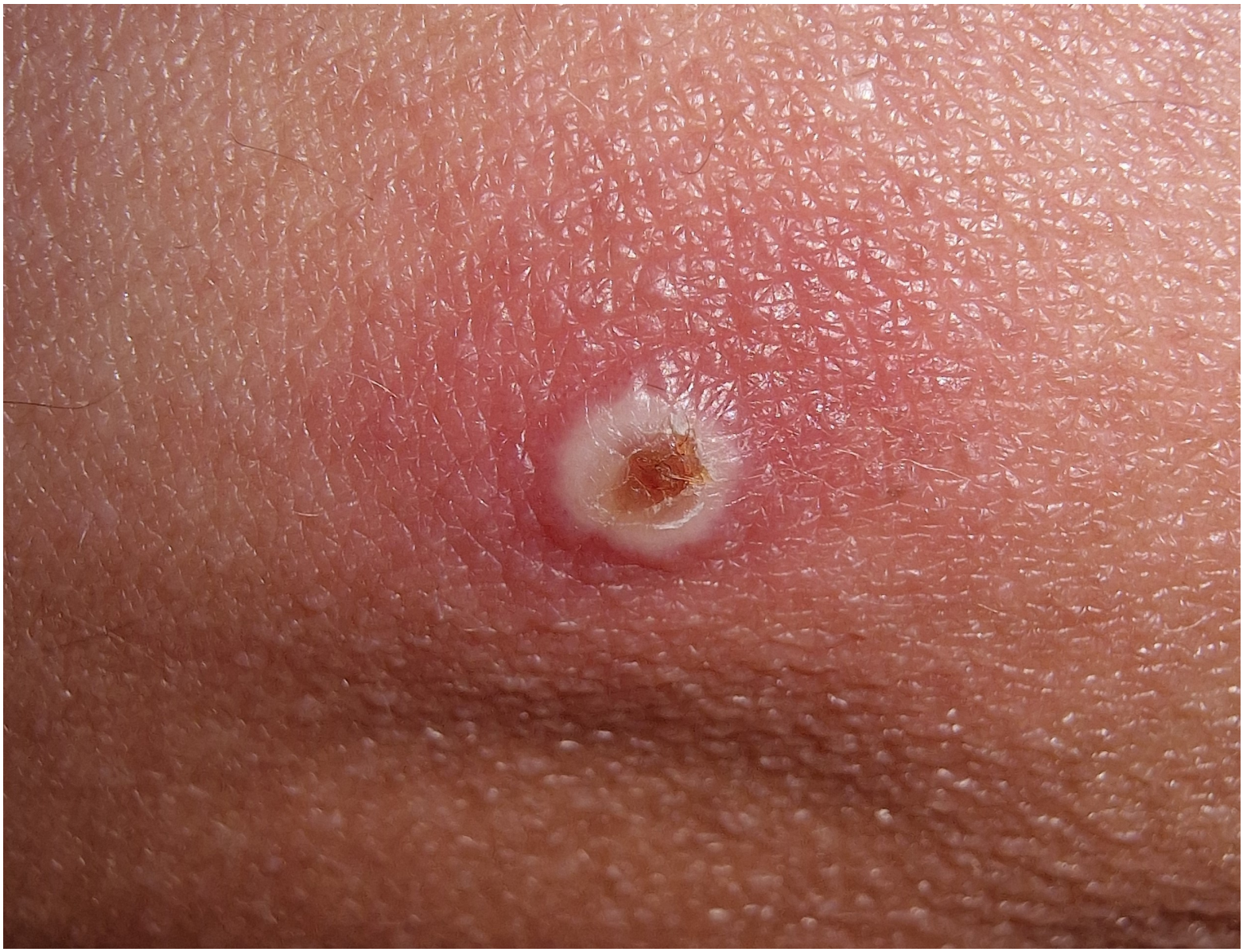
Figure 4. Tonsillar ulcer. These ulcers have surrounding edema and might have a higher risk of complications. They cause dysphagia and might potentially obstruct the airway.

Table 1. Description of the patients.

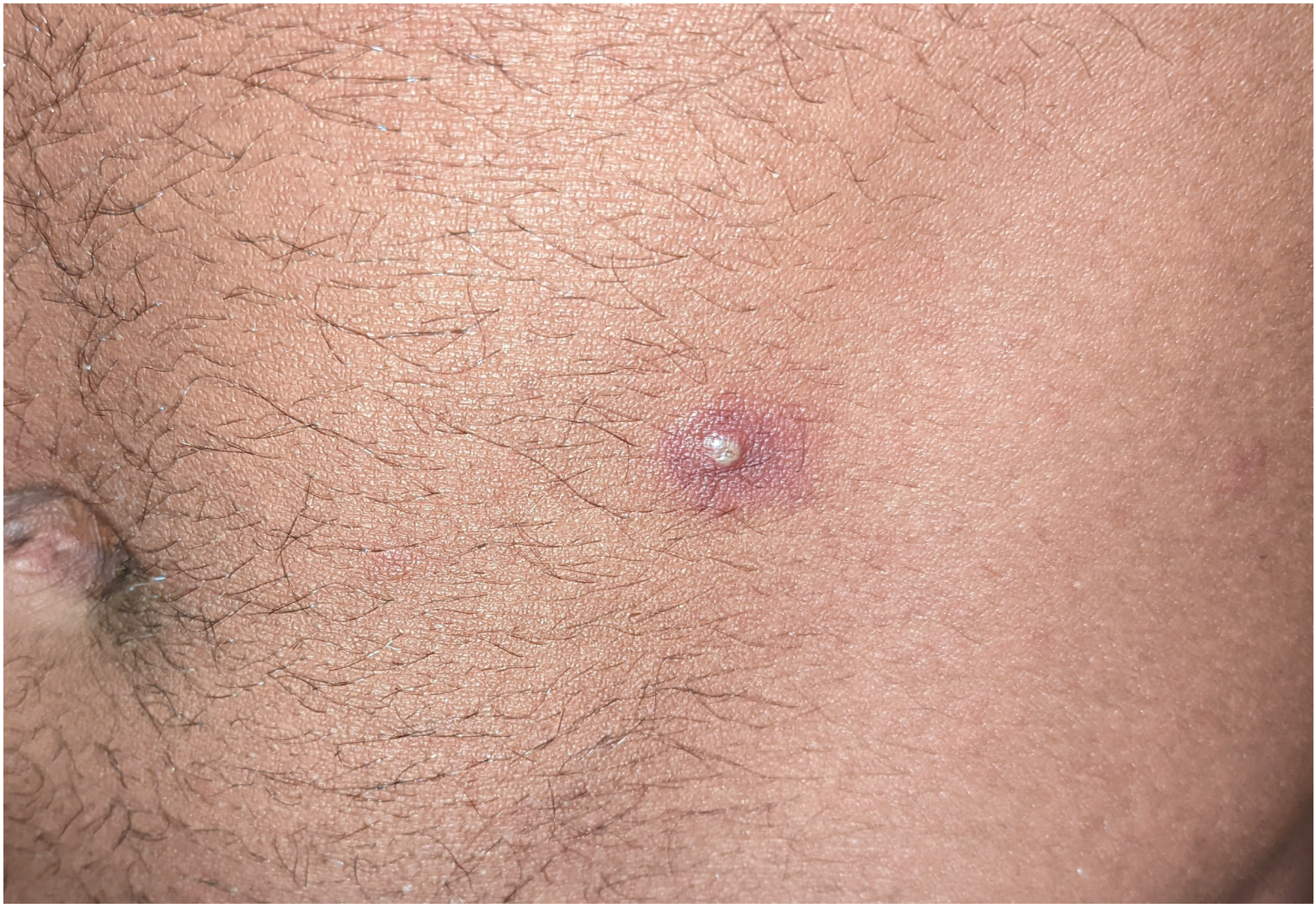
Number of patients	185
Age (years), mean (SD)*	38.7 (8.2)
Gender, (n (%))	
Male	185 (100%)
Female	0 (0%)
Transexual male	0 (0%)
Transexual female	0 (0%)
Other	0 (0%)
Previous history of smallpox vaccination	
Unknown	20 (11%)
No	145 (78%)
Yes (scar/other evidence)	20 (11%)
Born before 1972 (large decrease in smallpox vaccination)	
Yes	19 (10%)
HIV infection	
Yes	78 (42%)
CD4 count (cells/mm^3) (median, (p25-p75))	698 (549-930)
C4 nadir (cells/mm^3) (median, (p25-p75))	396 (249-575)
Detectable viral load (n=63)	6 (8%)
Required hospitalization	4 (2%)
Required intensive care	0 (0%)
Death*	0 (0%)
Clinical findings: cutaneous lesions (n, %)	
Type of exanthem	
Macular	12 (6%)
Papular	90 (49%)
Vesicular	54 (29%)
Pustular or pseudopustular	138 (75%)
Location of pustules-pseudopustules	
Genital	98 (53%)
Face	72 (39%)
Arms-Dorse of hands	70 (38%)
Perianal	62 (34%)
Legs	52 (28%)
Thorax	47 (25%)
Groin or pubis	30 (16%)
Abdomen	29 (16%)
Back	28 (15%)
Mouth	26 (14%)
Plant	22 (12%)
Palm	12 (6%)
Eyelids	2 (1%)

Number of affected areas	
1	53 (29%)
2	34 (18%)
3	34 (18%)
4 or more	64 (35%)
Number of lesions	
1	21 (11%)
2-25	152 (82%)
26-100	11 (6%)
>100	1 (1%)
Where all cutaneous lesions at the same stage? (Same morphology) (n=152)	
Yes	71 (47%)
No	81 (53%)
Clinical findings: extracutaneous	
Timing of events	
Exanthema before first symptom	4 (2%)
Exanthema and symptoms the same day	114 (62%)
Exanthema after first symptom	67 (36%)
Extracutaneous manifestations	
None	0 (0%)
Lymphadenopathy	104 (56%)
Fever	100 (54%)
Asthenia	81 (44%)
Myalgia	81 (44%)
Headache	59 (32%)
Proctalgia-proctitis	40 (22%)
Throat ache	34 (18%)
Arthralgia	21 (11%)
Lumbar pain	12 (6%)
Oral ulcer	10 (5%)
Abdominal pain	0 (0%)
Vomit	0 (0%)
Epidemiological findings	
Incubation period (days from suspected infection to first sign/symptom) (Median, (p25-p75)) (n=77)	6 (4-9)
Origin	
Imported	7 (4%)
Spain	176 (95%)
Unknown	2 (1%)
Travel outside the home town/city in the three weeks before first sign/symptom	
Yes	51 (28%)
Source of exposure	1 (1%)
Professional (health worker)	43 (23%)
Other contact with a case	82 (44%)

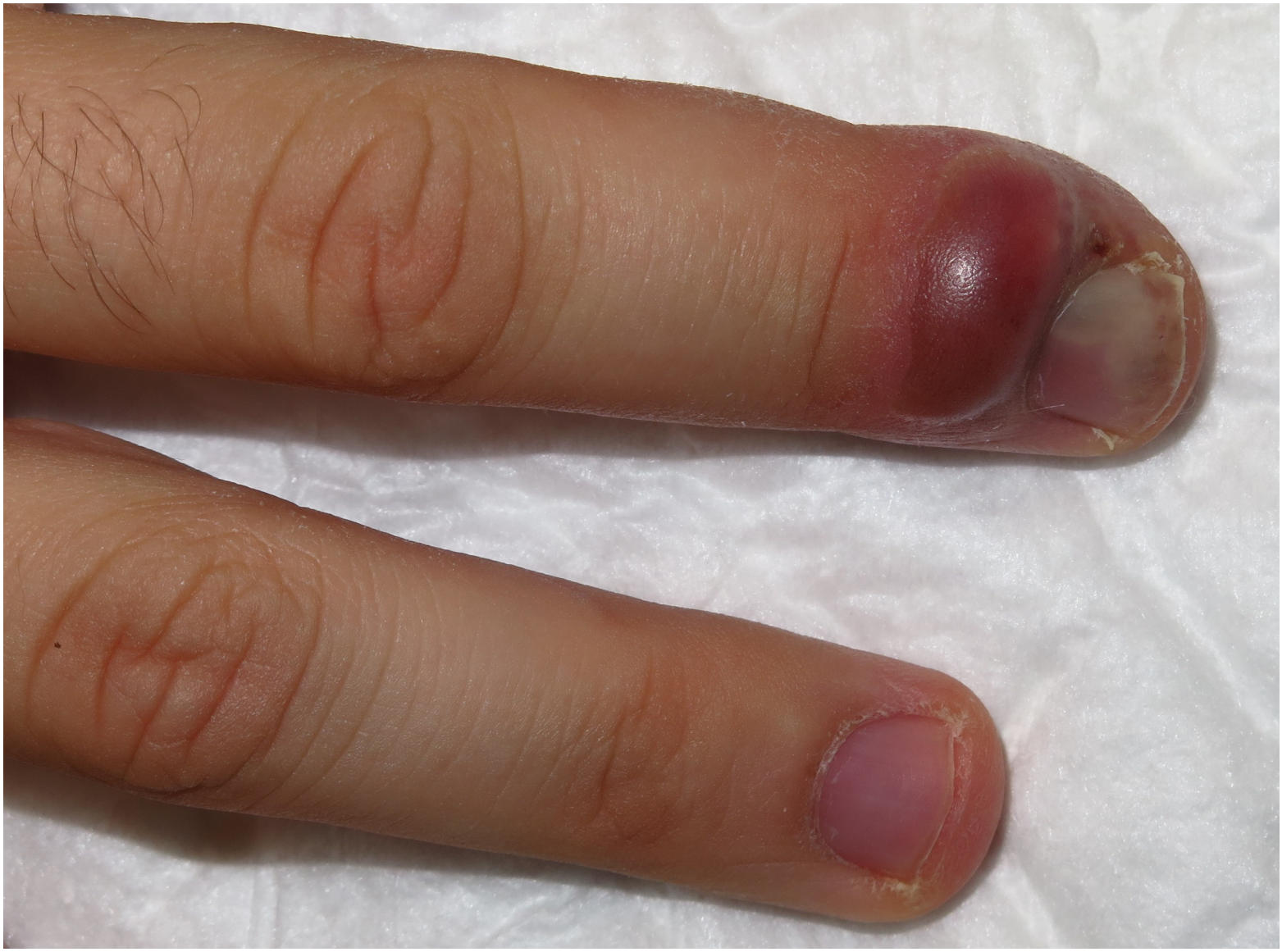
Unknown or no contact	
Type of case	
Isolated	48 (26%)
Index case	70 (38%)
Secondary case	67 (36%)
Patient describes himself as having sex with (could be more than one answer)	
Males	184 (99%)
Female	7 (4%)
Transexual male	1 (1%)
Transexual female	1 (1%)
Other	0
Number of sexual partners in the previous 2 weeks (median, (p25-p75))	3 (1-5)
Number of sexual partners in the previous 3 months (median, (p25-p75))	8 (4-17)
Use of social networks to meet partners	102 (55%)
Sex in a different country in the previous 3 months	23 (12%)
Sex with sex workers in the previous 3 months	11 (6%)
Use of drugs during sexual relationships in the previous 3 months	62 (34%)
Diagnosis of a sexually transmitted disease in the last year	100 (54%)
Other STD in screening	140 (76%)
Pets in the household	28 (15%)
Exotic pets in the household	16 (9%)



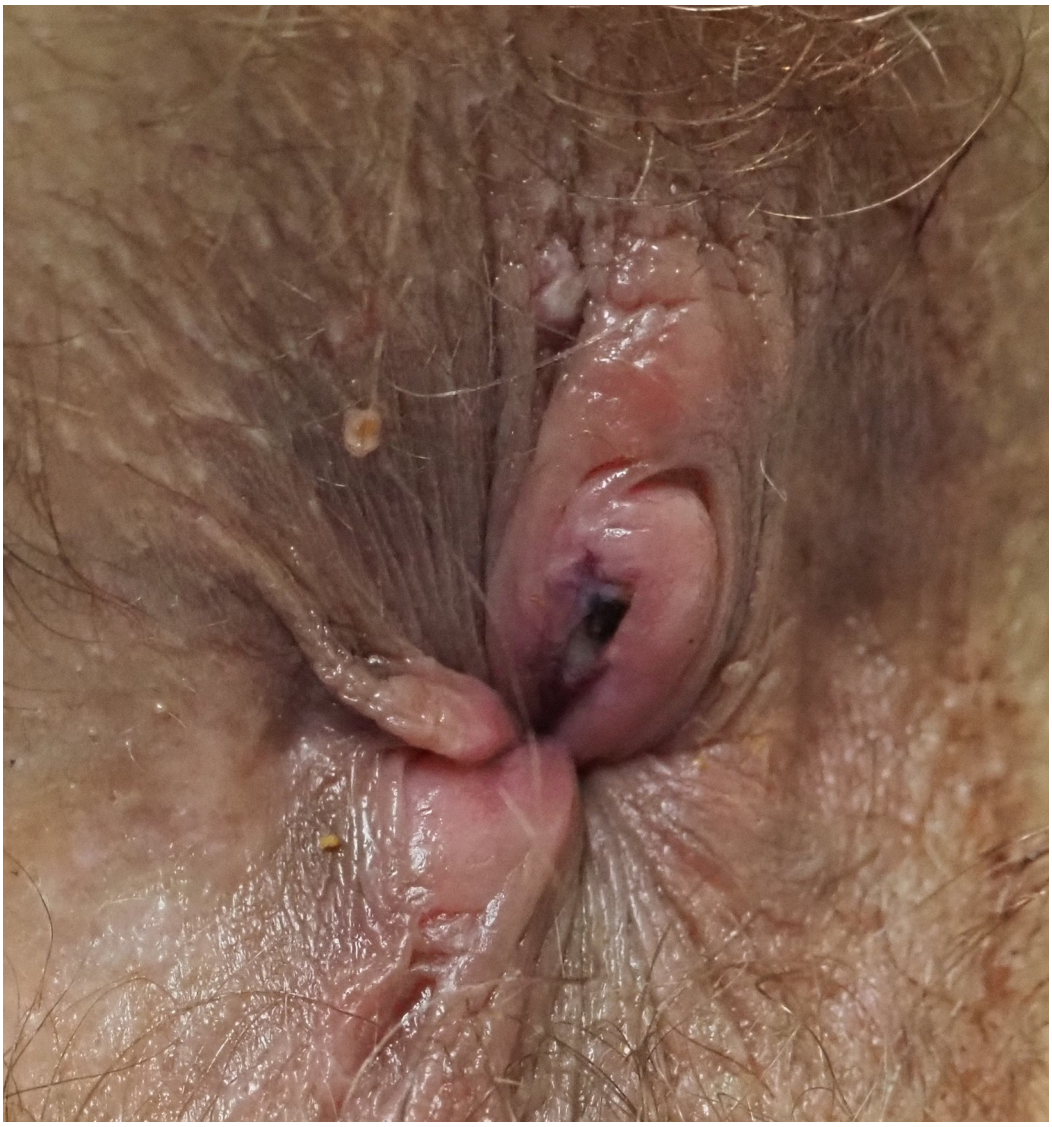
BJD_21790_Fig 1A.jpg



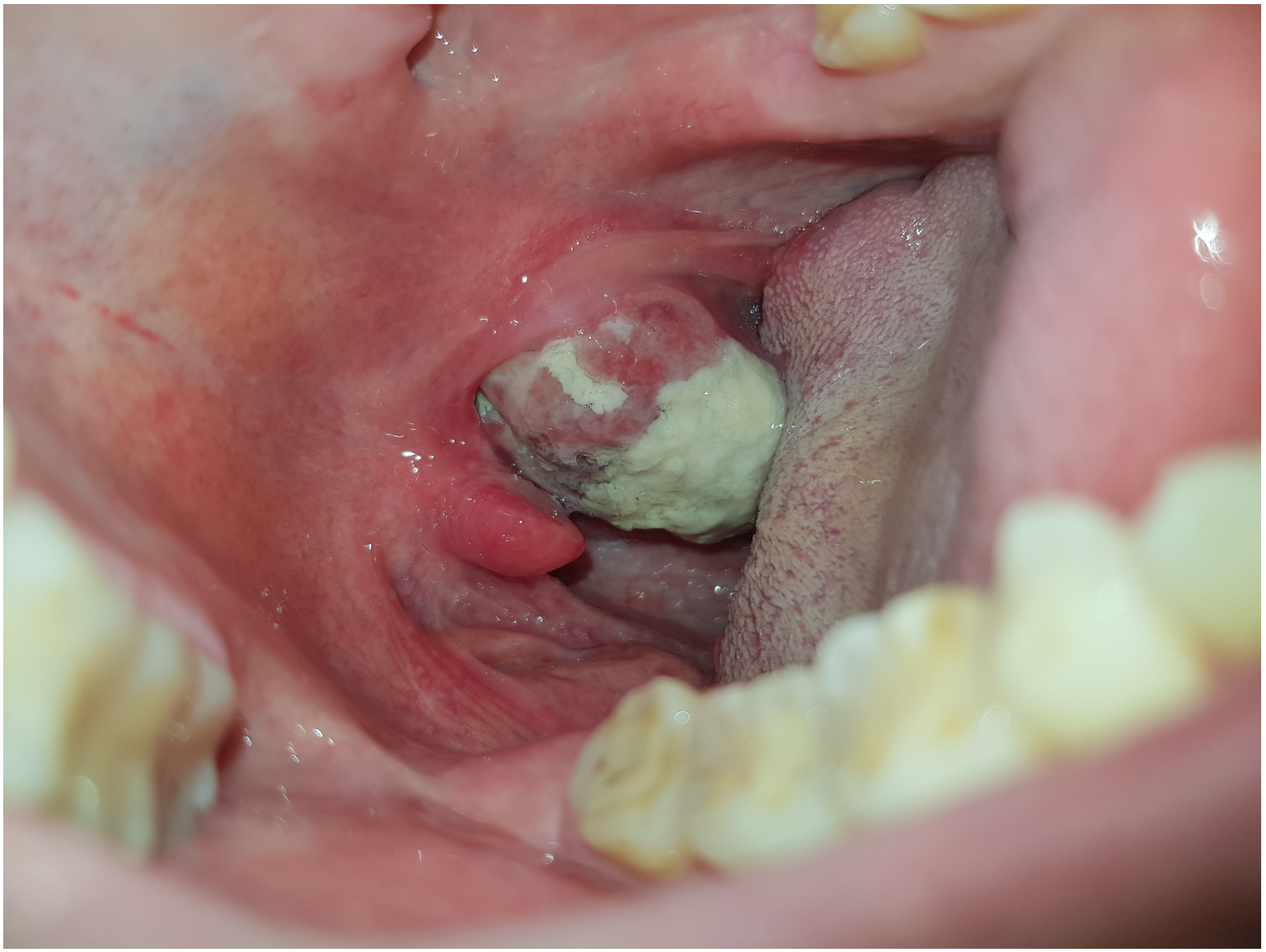
BJD_21790_Fig 1B.png



BJD_21790_Fig 2.jpg



BJD_21790_Fig 3.jpg



BJD_21790_Fig 4.jpg