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Fatal borealpox in an immunosuppressed patient treated with antivirals and vaccinia immunoglobulin — Alaska, 2023

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Abstract

Background: *Boreapox virus* (BRPV, formerly known as *Alaskapox virus*) is a zoonotic member of the *Orthopoxvirus* genus first identified in a person in 2015. In the six patients with infection previously observed BRPV involved mild, self-limiting illness. We report the first fatal BRPV infection in an immunosuppressed patient.

Methods: A man aged 69 years from Alaska's Kenai Peninsula was receiving anti-CD20 therapy for chronic lymphocytic leukemia. He presented to care for a tender, red papule in his right axilla with increasing induration and pain. The patient failed to respond to multiple prescribed antibiotic regimens and was hospitalized 65 days postsymptom onset for progression of presumed

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infectious cellulitis. BRPV was eventually detected through orthopoxvirus real-time polymerase chain reaction testing of mucosal swabs. He received combination antiviral therapy, including 21 days of intravenous tecovirimat, intravenous vaccinia immunoglobulin, and oral brincidofovir. Serial serology was conducted on specimens obtained posttreatment initiation.

Findings: The patient's condition initially improved with plaque recession, reduced erythema, and epithelization around the axillary lesion beginning one-week post-therapy. He later exhibited delayed wound healing, malnutrition, acute renal failure, and respiratory failure. He died 138 days postsymptom onset. Serologic testing revealed no evidence the patient generated a humoral immune response. No secondary cases were detected.

Conclusion: This report demonstrates that BRPV can cause overwhelming disseminated infection in certain immunocompromised patients. Based on the patient's initial response, early BRPV identification and antiviral therapies might have been beneficial. These therapies, in combination with optimized immune function, should be considered for patients at risk for manifestations of BRPV.

Summary:

An elderly, immunocompromised man in Alaska, USA, died from disseminated borealpox virus (BRPV) infection despite antiviral treatment. This case highlights BRPV's potential for severe disease in immunosuppressed individuals and the need for early detection and intervention.

Borealoxy virus (BRPV, formerly known as *Alaskapox virus*) is a member of the *Orthopoxvirus* genus first identified in a person in 2015 (AK2015_poxvirus) and small mammals in 2020.¹ Evidence suggests BTRPV is zoonotic and maintained among Alaskan small, mammal reservoirs and is phylogenetically differentiated based on geographic location.² Before December 2023, all six reported infections occurred among residents of the Fairbanks, Alaska, area and involved self-limiting illness consisting of a localized skin lesion and lymphadenopathy.³ In this report, we describe the clinical course of the first fatal case of BRPV infection, the experience of antivirals and vaccinia immune globulin used to treat borealpox disease, and summarize associated clinical findings.

Case Description

In September 2023 a man aged 69 years with chronic lymphocytic leukemia (CLL) and treated with venetoclax, monthly rituximab and intravenous immunoglobulin (IVIG) infusions, and oral acyclovir prophylaxis presented to a community health clinic. He was complaining of 5 days of subjective fever, headaches, and myalgias and 4 days of new skin lesions. The patient did not work and lived alone on a property surrounded by boreal forest on the Kenai Peninsula. He reported caring for a stray cat that regularly hunted small mammals and frequently scratched the patient. He reported no travel outside the Kenai Peninsula during the month before illness onset. Examination on day of illness (DOI) #6 revealed two, small, hard, disk-like lesions in the right axilla and right inner thigh (Figure 1). The axillary lesion was unroofed, swabs were sent to a commercial laboratory for bacterial and viral cultures, and he was treated with doxycycline. Bacterial cultures returned with a mixture of skin flora; no further species identification was sought. No virus was isolated from viral culture. A summary of pertinent diagnostic tests is presented in Table 1.

The following week, he was admitted twice to a local hospital with presumed bacterial pneumonia (cough and dyspnea) and received a combination of ceftriaxone, azithromycin, and levofloxacin. His cough and dyspnea resolved, but the right axillary lesion continued to enlarge. Three weeks after initial presentation (DOI #27), a punch biopsy was performed and revealed necrotic debris with spongiosis and apoptotic keratinocytes. No definite viral cytopathic changes were identified, and periodic acid-Schiff stain was negative for fungal hyphae. His monthly rituximab infusions were discontinued.

Despite interval treatment with vancomycin and trimethoprim/sulfamethoxazole, his axillary lesion worsened. Two months after initial presentation, he was again admitted to a local hospital (DOI #65). The right axillary lesion measured 22x11 cm and extended from the right upper back to the anterior chest. He was afebrile with normal vital signs. The white blood cell (WBC) count was 7.1 K/uL with 19% eosinophils (absolute eosinophil count 1,360 K/uL) and the C-reactive protein (CRP) was 111 mg/L. He underwent open biopsy; intraoperatively, no gross purulence was found. Microscopic evaluation revealed necrotic skeletal and fibroadipose tissue with focal acute and chronic inflammation but no evidence of malignancy. Bacterial cultures grew only *Staphylococcus epidermidis*. The patient was subsequently transferred to a referral hospital for further evaluation (DOI #80).

On arrival at the referral hospital, the body temperature was 37.2° C, pulse 84 beats/minute, respiratory rate 20/minute on room air, oxygen saturation of 96% by pulse oximetry, and blood pressure 144/53 mm Hg. The right axillary soft tissue lesion was extremely indurated but demonstrated only mild erythema. The open biopsy site was nonhealing and draining copious serous fluid with a surrounding gray coalescent plaque. The medial right thigh lesion was observed to have healed and scarred. A diffuse, macular rash on his torso and upper extremities was present. WBC was 6.98 K/uL (12% eosinophils), CRP 93 mg/L, creatinine 10.5 mg/dL and alanine aminotransferase 10 U/L (Appendix, Table S3). Contrasted computed tomography (CT) imaging of the chest performed at the referral hospital and magnetic resonance imaging of the right shoulder performed just before transfer (Figure 2) revealed myositis of the right trapezius and rotator cuff musculature.

An extensive list of laboratory tests was performed. *Toxoplasma*, *Bartonella*, and *Francisella* serologies were negative. Given strong suspicion that a highly unusual infectious process was occurring, a plasma microbial cell-free DNA metagenomic sequencing assay performed by Karius, Inc (Redwood City, California)⁴ was requested and ultimately reported 32,258 molecules per microliter (MPM) of cowpox virus (reference <10 MPM) on DOI #87 (Appendix, Table S1/Figure S1). The patient was placed into contact and airborne isolation. An additional swab was collected from the axillary wound and sent to the Alaska State Public Health Laboratory (ASPHL). The specimen tested positive on a generic orthopoxvirus polymerase chain reaction (PCR) assay but negative on the CDC 510(k) cleared non-variola orthopoxvirus PCR assay with ability to detect cowpox, mpox, and vaccinia viruses but not borealpox virus.⁵ Treatment for a presumed disseminated orthopoxvirus infection was initiated. Specimens were forwarded to the Centers for Disease Control and Prevention (CDC) for confirmatory testing. Generic orthopoxvirus DNA sequences were amplified, and viable virus was successfully cultured from the specimen.^{5,6} Sequence analysis demonstrated high identity (99.7%) to AK2015_poxvirus

strain, confirming the patient was infected with BRPV. BRPV from this patient was genetically divergent from the previous six BRPV isolates from persons and animals collected near Fairbanks, Alaska, with 623 single nucleotide polymorphisms (SNPs) and 82 insertion or deletion mutations relative to the AK2015 isolate. No predicted amino acid changes in the target of tecovirimat, Vaccinia virus Copenhagen (VACV-COP F13 ortholog, also known as VP37), relative to other BRPV F13 sequences were reported. Additionally, a 2-nucleotide insertion resulted in a frame shift and loss of thymidylate kinase (VACV-COP-A48R ortholog); loss of A48R results in virus attenuation in vaccinia virus.⁷

Tissue samples from the axillary lesion collected by open biopsy at the local hospital and repeat samples collected by CT-guided needle biopsy at the referral hospital were sent to CDC and revealed geographic necrosis, and eosinophilic and histiocytic inflammation with confirmed immunohistochemical (IHC) evidence of an orthopoxvirus (Figure 3; see Appendix for technical details).

A detailed dermatologic examination revealed previously unrecognized small lesions that were crusted and raised on the patient's central occiput, left upper lip, right palmar fifth finger, right forehead, and left medial distal thigh and injected sclera bilaterally. He recalled receiving smallpox vaccine as a child, but a vaccination scar was not identified. An ophthalmologist exam identified only mild crusting and trace left-sided conjunctival injection; a conjunctival swab was PCR-positive for orthopoxvirus. The patient was given 200 mg of IV tecovirimat every 12 hours for 21 days. Two doses of intravenous vaccinia immunoglobulin (VIGIV) 9,000 IU/KG were administered on days 5 and 6 of therapy, and doses of oral brincidofovir 200mg were added on days 7 and 14. On day 2 of tecovirimat therapy, the patient exhibited a brief episode of rigors and decreased attentiveness that resolved with pause of the infusion and intravenous diphenhydramine administration. The infusion was subsequently reinitiated and tolerated for the remainder of the treatment course.

Approximately one week into tecovirimat therapy, the patient's condition gradually improved with plaque recession and early re-epithelization around the axillary lesion margin. The conjunctival injection also improved. Sera collected after vaccinia immunoglobulin treatment was positive for anti-orthopoxvirus IgG antibodies but negative for IgM by enzyme-linked immunosorbent assay (ELISA).⁸ His arm edema slowly decreased, and the maculopapular rash resolved. However, peripheral eosinophilia persisted (Appendix, Table S3).

The patient was transferred to a long-term acute care hospital for ongoing wound care and physical and nutritional therapy (DOI #108). Mandated intake testing of a nasal swab for SARS-CoV-2 was incidentally positive by RT-PCR and he was treated with 0.5 g/kg of IVIG and 5 days of intravenous remdesivir. He reported minimal cough, did not require oxygen, and his respiratory symptoms resolved. Despite improving lesions, he demonstrated no healing of the open biopsy incision that continued to drain serous fluid. He did not tolerate attempts at nasogastric feeding. Pain in his right shoulder and arm was inadequately relieved with opiate medications, and the receipt of these medications coincided with waxing and waning delirium. On DOI #136, he was noted to have new lesions on the left posterior thigh, left neck, and bilateral shoulders. He developed increasing somnolence, leukocytosis,

and renal failure on DOI #137, which progressed to hypoxic respiratory failure despite broad-spectrum antimicrobials. After 72 days of uninterrupted hospitalization, he died on DOI #138 (Appendix, Figure S2). A postmortem examination was performed and identified disseminated BRPV. Diffuse macular and pustular skin lesions of variable age and size were observed macroscopically, including on the axilla, superior and posterior shoulder, posterior neck, upper back, forehead, retroauricular area, occipital area, posterior thigh, buttock, medial knee, and radial forearm. Viral antigens and DNA were found in nearly all evaluated tissues by laboratory-developed assays (22 of 23 specimens; IHC: 14/23, 61%; DNA in-situ-hybridization: 18/18, 100%). Additionally, histopathologic examination revealed presence of microvascular thrombosis, tissue necrosis, and histiocytic and eosinophilic cellular infiltrates in multiple organs. Histopathologic findings on autopsy are pending.

Discussion

This is the first fatal case of BRPV infection and described experiences using antivirals and vaccinia immunoglobulin for treatment of BRPV. Multiple novel clinical aspects of this case are present that warrant discussion.

First, like other orthopoxviruses, BRPV has now been demonstrated to cause overwhelming disseminated infection among certain immunocompromised hosts. The patient was receiving monthly infusions of anti-CD20 therapy for CLL. Anti-CD20 therapy is associated with numerous opportunistic infections, including severe varicella zoster, pneumocystis, toxoplasmosis, and JC polyomavirus progressive multifocal leukoencephalopathy.^{9–11} Mpox is particularly threatening among persons with severe immunocompromise (e.g., patients with congenital immunodeficiencies, solid organ transplantation, or most commonly during the global outbreak, HIV CD4+ T-cell counts <200); in these patients, high rates of uncontrolled viral replication have sometimes resulted in death after protracted hospital courses.^{12–15} Whether anti-CD20 therapies can cause the degree of immunocompromise associated with other orthopoxvirus deaths is unclear; other published reports of severe mpox or cowpox in immunocompromised patients receiving rituximab were not found.¹⁶ Based on known importance of both neutralizing IgG antibodies and poxvirus-specific Th1 responses in control of viral replication,¹⁷ a hypothesis was developed that the patient's immunodeficiency related to CD20 depletion therapy contributed to his demise. Serial serum assays revealed no evidence of anti-orthopoxvirus IgM production while IgG levels, likely attributable to VIGIV infusions, waned after therapy suggesting that the patient was unable to mount an effective humoral defense. The severe viral lesions seen at autopsy confirm ability of this virus to impart devastating injury to multiple organs and directly contributed to his death.

Second, treatment with intravenous tecovirimat, vaccinia immunoglobulin, and brincidofovir appeared to transiently halt viral activity. One week after initiation of therapy his cutaneous lesions began to crust and heal with some new epithelialization along the wound margins. Improvement began after tecovirimat and VIGIV were administered and coincident with the initiation of brincidofovir. In total, 40 amino acid changes are described between BRPV F13 (the viral target of tecovirimat) and mpox virus F13 (2022 outbreak Clade IIb). Most of these mutations are not near the predicted drug binding site, and none of the specific amino

acid changes reported in BRPV have been associated with resistance.^{18,19} *In vitro* testing confirmed efficacy of tecovirimat to inhibit BRPV (Appendix). However, like the challenges associated with treating mpox patients with severe immunocompromise, extended courses of tecovirimat might lead to resistance. While the lack of predicted amino acid changes observed in this patient suggests lack of resistance, recovery of the patient's own immune system would have been essential to recovery. Antivirals (e.g., tecovirimat or brincidofovir) are viristatic and require concomitant immune optimization, which is difficult to achieve after rituximab. Optimal therapy for severe BRPV has yet to be defined, but this experience suggests combination antiviral therapy likely led to an initial clinical response. Given the relapsing cutaneous lesions immediately preceding death, three weeks of therapy might be inadequate among immunocompromised hosts; aside from a single episode of brief rigors during the third tecovirimat infusion, the therapies were well tolerated.

Third, identification of BRPV presents a diagnostic challenge. On arrival at the referral hospital, clinical evidence was available that a dramatic and unusual process was occurring in the right axilla. However, the etiology was not obvious and no clear evidence of disseminated infection was initially recognized. Because the patient resided in an area of Alaska approximately 570 miles south of where all previously identified borealpo cases had occurred, the diagnosis was not considered. Ultimately a microbial cell-free DNA metagenomic sequencing assay from a commercial laboratory (Karius, Inc.)²⁰ was able to confirm an orthopoxvirus diagnosis. However, because of limited comparator BRPV sequences, the specimen was initially incorrectly diagnosed as cowpox, a closely related orthopoxvirus. This occurred after collaboration from ASPHL and CDC after the patient was hospitalized. Alaskan clinicians in areas with the potential for novel zoonotic spillover events should remain vigilant for unusual infectious presentations and consider a broad differential diagnosis, including orthopoxvirus infection. State public health departments are familiar with appropriate testing methods given the 2022 mpox outbreak of global concern²¹ and can facilitate rapid orthopoxvirus PCR testing. Early identification and therapy might result in improved outcomes in patients with severe BRPV.

Multiple limitations of this report are noted. First, the patient's source of BRPV infection is unknown. He cared for a stray cat that hunted small mammals regularly; all prior borealpo cases reported contact with domestic pets, the majority owning a cat or dog. In January 2024, the stray cat tested negative for anti-orthopoxvirus antibodies by ELISA and orthopoxvirus DNA by PCR. Despite these results, direct inoculation from a scratch or other fomite contamination originating from the cat remains plausible. Cowpox virus is endemic in northern Europe and human disease is frequently associated with domestic cats,^{22–24} suggesting a similar mechanism might exist with BRPV. The patient did not report a recent travel history before illness onset. Additionally, the polymorphisms observed in the BRPV sequence obtained from the patient and its agreement with previous knowledge that orthopoxviruses generally differentiate based on their geographic location.²⁵ This suggests the patient's infection was locally acquired from direct contact with an animal near his home. As such, testing of small mammals in the Kenai Peninsula is needed to characterize BRPV's animal reservoir(s) in the area. Second, we were unable to test pretreatment serum samples for anti-orthopoxvirus antibodies, thus limiting our understanding of the serological kinetics given confounding inherent to VIGIV infusions.

Third, we were unable to determine the risk for human-to-human transmission of BRPV without extensive serologic investigation of his numerous contacts. However, he had repeated close contact with healthcare personnel for approximately two months before diagnosis and no secondary clinical cases were reported. He was not placed into contact isolation (and briefly airborne isolation) until after diagnosis, suggesting BRPV is poorly adapted for human-to-human transmission and that standard precautions alone are likely adequate in most circumstances.²⁶ Moreover, no evidence of secondary transmission with any of the six prior cases of borealpox was reported and each displayed a localized, self-resolving infection. Nonetheless, findings from this case warrants increased statewide awareness among clinicians regarding BRPV and its clinical presentations, especially while the virus's transmission routes and distribution in small mammal reservoirs remain unclear.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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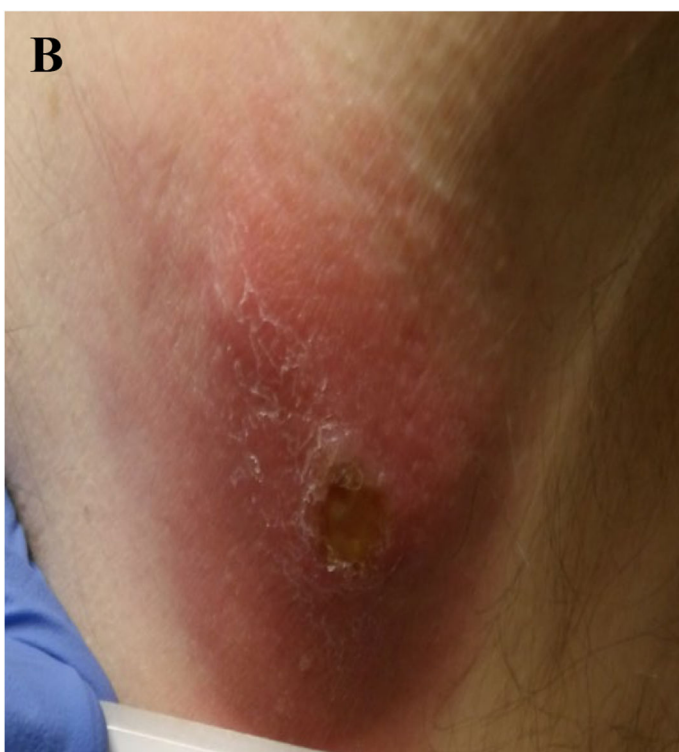






Figure 1: Progression of primary right axilla lesion

(A) At time of presentation (day of illness, [DOI] #6). (B) At time of punch biopsy [DOI #27]. (C) At time of regional hospitalization [DOI #65]. (D) Eight days into tecovirimat initiation [DOI #95]. (E) At time of tecovirimat completion [DOI #106].

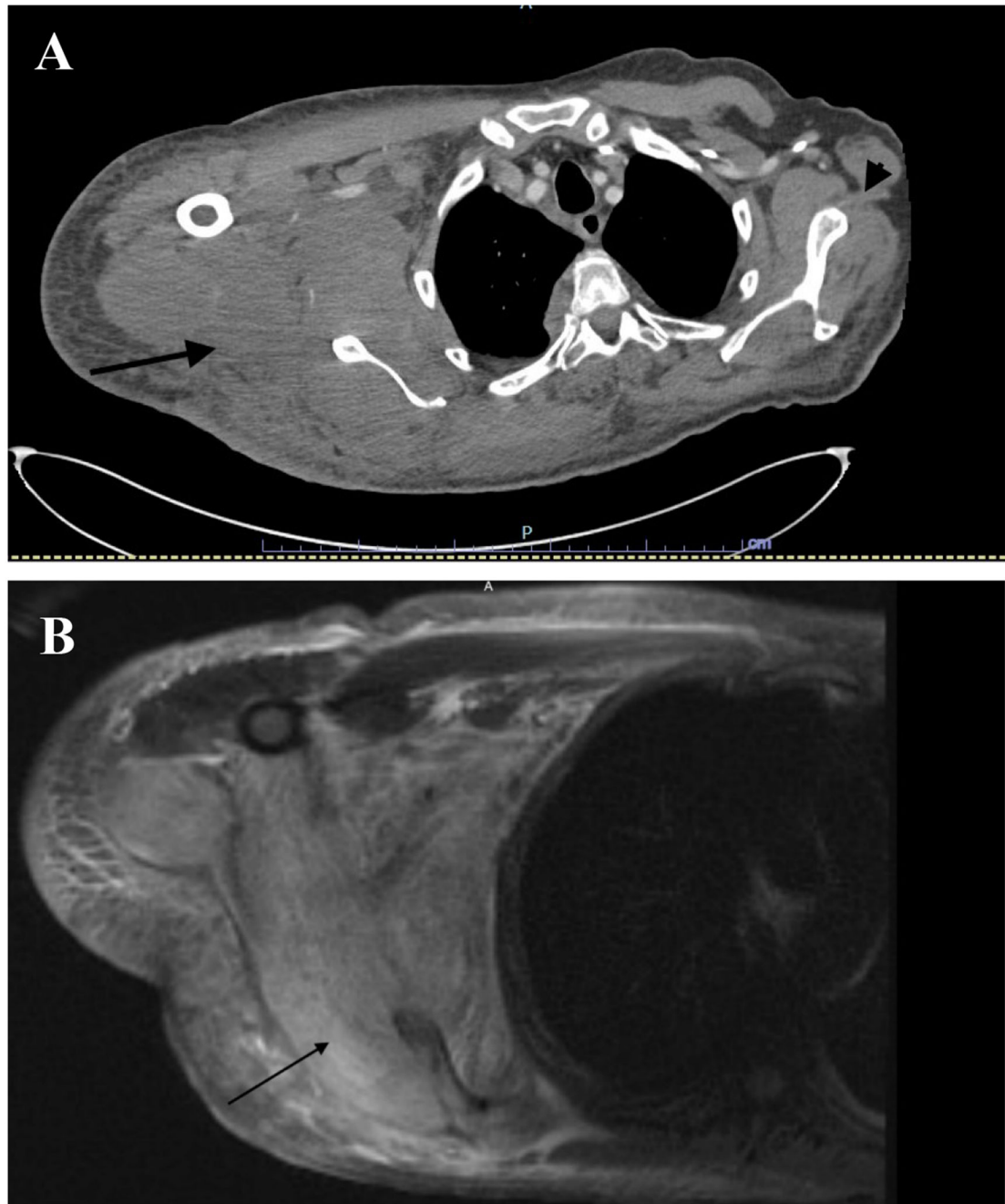


Figure 2: Patient's medical imaging at referral hospital

(A) Contrast-enhanced computed tomography scan of the chest day of illness [DOI] #81 showing severe enlargement and myositis of the right shoulder musculature (arrow) and normal left shoulder musculature (arrowhead). (B) T2 weighted magnetic resonance imaging of the right shoulder [DOI #79] demonstrated marked enlargement and edema of the rotator cuff musculature.

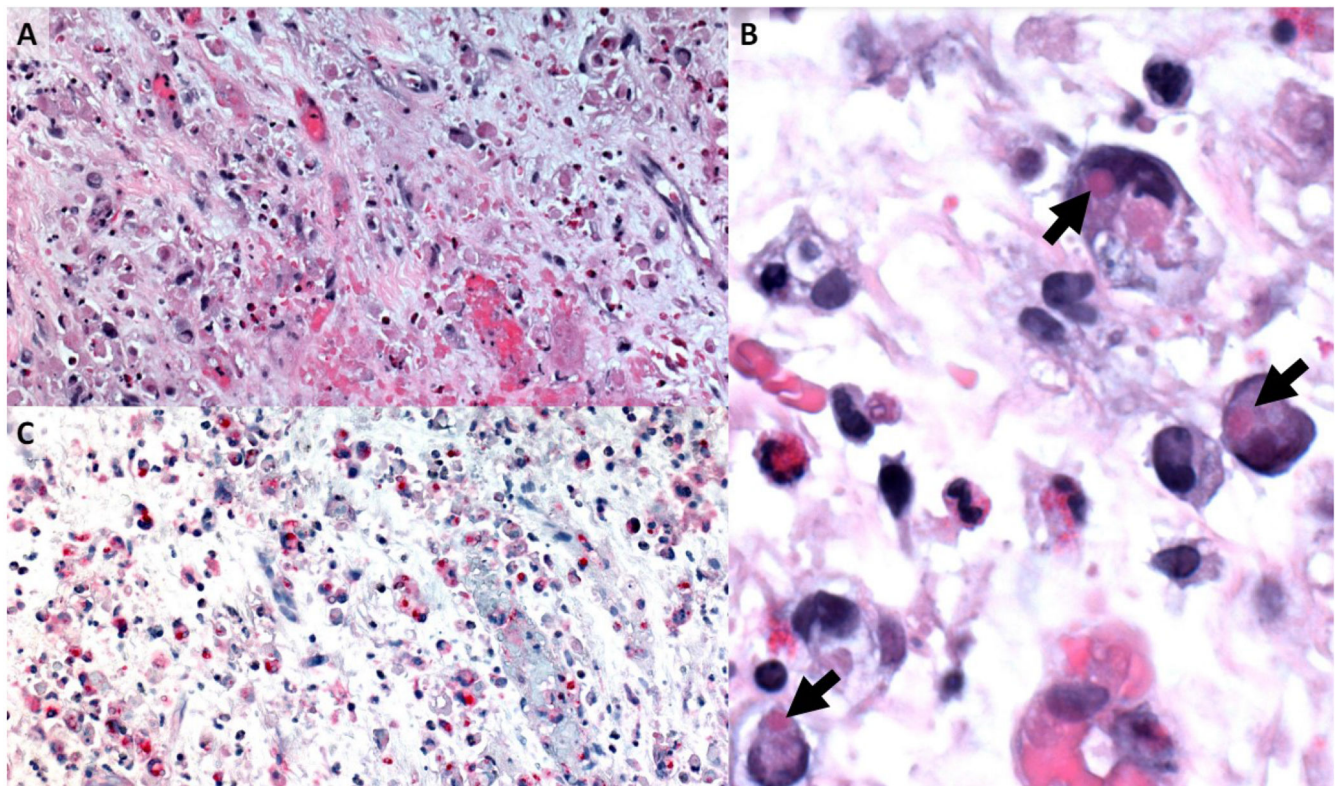


Figure 3: Histopathological findings in a soft tissue biopsy

(A) Hematoxylin and eosin (H&E)-stained tissue sections of the axillary soft tissue core needle biopsy revealed presence of loose connective with areas of geographic necrosis, and chronic histiocytic and eosinophilic inflammation. (B) Within the necrotic areas, cells with viral cytopathic changes and intra-cytoplasmic large eosinophilic inclusions (arrows) are identified. (C) An immunohistochemical assay generated against monkeypox virus but which is broadly reactive with other orthopoxviruses, highlighted immunoreactive cells in the areas of inflammation and necrosis.

Table 1:

Key clinical diagnostic tests

Pathogen or Target	Test	Type of Sample	Day of Illness Specimen Collected	Result
Viruses	Viral culture, general	Deroofed axilla lesion	6	No virus isolated
Bacteria	Anaerobic and aerobic culture	Deroofed axilla lesion	6	Mixed skin flora
Bacteria	Culture	Right axilla soft tissue excisional biopsy	66	4+ oxacillin resistant <i>Staphylococcus epidermidis</i>
Bacteria	Anaerobic culture	Tissue	66	No organisms isolated
<i>Toxoplasma gondii</i>	Antibody, qualitative	Blood	82	IgG Negative
<i>Francisella tularensis</i>	IFA *	Blood	81	IgG and IgM negative
<i>Bartonella henselae</i> and <i>Bartonella quintana</i>	IFA	Blood	82	IgG and IgM Negative
Varicella zoster virus	NAAT †	Right axilla lesion swab	81	Negative
Microbes	mcDNA ‡	Plasma	82	Cowpox virus: 32,258 MPM § <i>Actinomyces oris</i> : 84 MPM <i>Rothia mucilaginosa</i> : 80 MPM <i>Streptococcus parasanguinis</i> : 62 MPM
Herpes simplex virus	NAAT	Right axilla lesion swab	85	Negative
<i>Treponema pallidum</i>	Antibody, qualitative	Blood	85	Negative
<i>Clostridioides difficile</i>	PCR ¶	Stool	90	Negative
Orthopoxvirus	IHC #	Right. Axilla soft tissue biopsy	86	Immunoreactive
Orthopoxvirus	IHC	Right axilla soft tissue excisional biopsy	66	Immunoreactive
Generic orthopoxvirus	PCR	Right axilla lesion swab	86	Positive
Non-variola orthopoxvirus	PCR	Right axilla lesion swab	86	Negative
Orthopoxvirus	Antibody	Blood	90	IgG positive **, IgM negative
Bacteria	Gram stain	Right axilla tissue	92	0-1 per low power field: white blood cells, polymorphonuclear 0-1 per low power field: Epithelial cells, squamous 4+ yeast
SARS-CoV-2	PCR	Nasopharyngeal swab	107	Positive
Orthopoxvirus	Antibody	Blood	111	IgG positive, IgM negative

* Immunofluorescence assay

† Nucleic Acid Amplification Test

‡ Microbial cell-free DNA

§ Molecules per microliter

¶ Polymerase chain reaction

Immunohistochemical assay

** Anti-orthopoxvirus IgG assay does not differentiate adaptive vs prophylactic antibodies. IgG positive likely due to intravenous vaccinia immune globulin administration.

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