Parapoxvirus Infections in the Country of Georgia: A Case Series

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Abstract. Infections caused by viruses of the parapoxvirus (PPV) genus, including orf and pseudocowpox viruses, are frequently seen in both humans and animals in many regions of the world. These infections are often misdiagnosed or neglected because of the lack of clinician awareness, inadequate diagnostic capacity, and their relatively mild disease presentation, which may result in affected individuals not seeking medical attention. Although PPV infections should be routinely considered in patients with cutaneous lesions, especially in those who have occupational exposure to farm animals, they are often excluded from the differential diagnosis because they are not perceived as serious, resulting in underestimation of the burden of disease. Since 2014, significant enhancements to Georgia's epidemiologic and laboratory capacity have made PPV surveillance and detection possible. In this study, we present information on 27 confirmed cases of PPV infection reported to Georgia's national surveillance system from January 2016 through January 2017.

INTRODUCTION

Parapoxvirus (PPV) infections commonly occur in animals, but are an underappreciated and underreported cause of cutaneous lesions in humans. Orf, bovine papular stomatitis virus, and pseudocowpox are PPVs that are known to infect sheep, goats, and cattle and other animals. Humans may also acquire PPV, often following direct contact with skin lesions from infected animals. Regular public health surveillance and reporting of human PPV infections is in place in many parts of the world, including Europe, and North and South America.^{1–5} Clinical manifestations of PPV in humans are similar to those in animals although they may vary depending on the specific type of PPV involved and typically present as vesiculoulcerative lesions of keratinized skin and mucosal surfaces.⁶ Infection with PPV is usually mild and self-limited with skin lesions generally resolving within 4–8 weeks,⁷ although reports exist of more aggressive cutaneous lesions occurring in immunocompromised individuals that can result in development of giant orf, multiple lesions, and persistent lesions which fail to resolve spontaneously.^{8–10}

Parapoxvirus may go under-recognized for a number of reasons, including its self-limited nature, the reduced likelihood that affected persons will present for medical evaluation, and clinicians' lack of familiarity with PPV-associated diseases.¹¹ The skin manifestations of PPV infections are nonspecific and may be misdiagnosed as cutaneous anthrax,¹² cutaneous leishmaniasis,^{10,13} or cowpox.¹⁴ Laboratory testing for PPV confirmation may not be available to clinicians even when it is suspected, and surveillance systems for reporting and monitoring the burden of disease are not in place for many countries and regions of the world.¹¹

The country of Georgia has a population of 3.7 million, with an area of 69,700 km² (roughly comparable with Ireland); 86.8% of the population is ethnic Georgians, 6.3% Azeri, and 4.5% Armenians.¹⁵ Georgia, which regained independence from the Soviet Union in 1991, is bordered by the Russian Federation on the north, by Turkey on the southwest, by Armenia on the south, and by Azerbaijan on the southeast (Figure 1). Currently, the

country is divided administratively into 11 regions and 67 districts, which are smaller administrative entities.¹⁶ Until recently, no cases of PPV had ever been reported from the country of Georgia although cutaneous human anthrax, for which PPV is often mistaken, has been reported as a significant public health issue for some time.¹⁷ Among countries that border Georgia, only Turkey has documented indigenous PPV infections characterized by transmission from animals to humans.^{5,12,18–20} Turkey has reported cases of PPV, including cases of orf virus, in humans since 2005^{5,12,19,20} and pseudocowpox virus in cattle identified in cattle in 2013.¹⁸ Given that PPV infections have been reported for a number of years from a neighboring country, it seems probable that PPV cases in both animals and humans have been present, but have gone undetected, in Georgia. The first detected Poxvirus in Georgia occurred in 2013 in the Akhmeta region and was confirmed as a novel orthopoxvirus (OPXV).²¹ This discovery elevated concerns about the potential for other poxviruses, resulting in greater availability of diagnostic tools and development of a national surveillance system for poxviruses, including PPV.

Epidemiologic surveillance of communicable diseases in Georgia is based on passive surveillance. All hospitals, state and private laboratories, and outpatient clinics are required to report to the local public health authorities within 24 hours once a notifiable disease is detected or suspected. Local public health authorities, working in collaboration with the National Center for Disease Control and Public Health (NCDC), are responsible for investigating the reported cases of notifiable diseases and registering cases in the Electronic Integrated Disease Surveillance System (EIDSS). The aim of EIDSS is to strengthen One Health disease surveillance by capturing human and animal disease and to support the implementation of International Health Regulations 2005.²² The list of notifiable diseases is approved by ministerial decree and currently includes 72 diseases. Following the identification of the novel OPXV in 2013,²¹ “diseases caused by poxviruses” were added to Georgia's notifiable diseases list.

The NCDC and the Richard Lugar Center for Public Health Research located in the capital, Tbilisi, have worked to increase nationwide awareness and strengthen surveillance for a number of infectious diseases, including those caused by PPV. The addition of poxviruses to the list of nationally reportable diseases in Georgia has led to a number of activities in the human and veterinary health sectors directed toward

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FIGURE 1. Parapoxvirus cases by region.

enhancement of the country's capacity to detect, diagnose, and report poxvirus infections. The aim of this study is to describe the epidemiology and clinical characteristics of select cases of PPV in Georgia using data from the country's newly expanded surveillance program.

MATERIALS AND METHODS

Data collection. Case-based data were extracted in January 2017 from the EIDSS, which has an open source software platform²³ that has been configured to meet existing local needs in Georgia, including disease-specific forms for notifiable illnesses. In 2004, at the time EIDSS was launched in Georgia, data collection was limited to three locations: NCDC's main office, Kutaisi Public Health Center, and the Laboratory of the Ministry of Agriculture. Since then, the system has expanded and currently exists in its sixth major version with incorporation into all public health centers, where data from respective districts and regions are collected providing coverage for the entire country (note that the Autonomous Republic of Abkhazia and Samachablo region are excluded because of existing territorial conflicts). The EIDSS network currently includes 190 reporting sites in Georgia, with 90 being under the authority of the Ministry of Health, Labor, and Social Affairs; another 97 under the Ministry of Agriculture; and three jointly operated by both ministries.²⁴

Country-wide surveillance for poxviruses was fully operational by January 2016. Cases included in this study were

human cases that were laboratory confirmed as PPV infection and were reported into the EIDSS database between January 29, 2016 and January 3, 2017. Case information is required for laboratory testing and is collected soon after an individual is identified as a suspect case by a physician. De-identified case-based information from EIDSS included demographic, clinical, laboratory, and categorical risk-factor data.

Specimen collection and laboratory testing. Clinical specimens were obtained from the skin lesions of cases through passive surveillance, by the attending physician at local medical facilities. After removing the lesion, sampling of the base was performed using a cotton swab. For confirmation of PPV infection, DNA samples were extracted using DNeasy Blood and Tissue Kit as per the manufacturer's instructions and tested by Taqman-based quantitative real-time polymerase chain reaction (PCR)²⁵ for the presence of genus DNA signatures from PPVs using ABI 7500 Fast Real-Time PCR instrument (Applied Biosystems, Foster City, CA). Testing was performed at the NCDC/Richard Lugar Center for Public Health Research in Tbilisi, Georgia.

Ethical considerations. Data were extracted from the EIDSS in such a manner that subjects cannot be identified and the NCDC's Institutional Review Board considered this research to be exempt.

RESULTS

Demographics. Twenty-seven individuals reported through the EIDSS systems met the case definition of laboratory-confirmed

PPV infection. Of these, 21 (74%) were initially diagnosed and reported by the attending physician as cutaneous anthrax, until diagnostic testing confirmed PPV. Demographic characteristics of cases are described in Table 1. Overall, more women (56%) than men were detected with PPV infection; the median age of all cases was 33 years (range 15–65 years). All but one of the 27 cases were residents of Georgia; the one nonresident from Azerbaijan was exposed while living in Georgia. Cases were reported from six regions with Imereti (10 cases), Kvemo Kartli (six cases), and Shida Kartli (five cases) being the most common (Figure 1); 18 different districts within these six regions had cases reported with the most frequent being Gori (four cases) followed by Terjola, Tskhaltubo, and Gardabani (three cases each). Twenty-one cases (78%) were ethnic Georgians, five (19%) were Azerbaijanis, and one (3%) was Armenian. The most common occupation reported by cases was housewife ($N = 13$, 48%), followed by farmer ($N = 4$, 15%), unemployed ($N = 3$, 11%), and student/school boy ($N = 2$, 7%) (Table 1).

Risk factors. Among the 27 confirmed cases of PPV, 85% had a known cow exposure and the remaining 15% were linked to a sheep exposure. Other exposures were not mutually exclusive and included contact with skin abnormalities on the animals described as sores, ulcers, or lesions ($N = 12$, 44%). When examining multiple exposures, the most common were milking cows ($N = 19$, 70%), cleaning farms ($N = 17$, 63%), and contact with animals with no identified skin damage or lesions ($N = 16$, 59%). All housewives reported milking cows as an exposure whereas only 43% of other occupations combined had milking as an exposure (Table 1).

Clinical presentation. All 27 cases were reported to have skin lesions with the most common presentations as pustules (52%) and ulcers (37%); five patients (19%) required hospitalization and no deaths were reported. Additional details of the hospitalization were not available in EIDSS. The mean number of days from clinical onset to diagnosis for all cases was 13.1 days (median 10, range 4–33 days). Among the 22

patients with information on date of presentation for clinical evaluation, the mean number of days between symptom onset and presentation was nine (median 6, range 2–26). The majority of cases (85.2%, $N = 23$) were uploaded into the EIDSS within 1 day of initial diagnosis, 7.4% ($N = 2$) between 2 and 3 days, and the remaining 7.4% ($N = 2$) required more than 2 days. Although the surveillance system does not collect specific details about the lesions, a number of common features were noted in the accompanying comments section, including: lesions were primarily located on hands and fingers; lesion edges appeared as both clean or ragged; most patients had a single lesion although, unusually, up to seven to eight were observed; lesions presented both as painful and painless in equal measure; the diameter of lesions typically ranged between 1 and 2.5 cm in the largest dimension and rarely exceeded this size; some of the most frequently described accompanying symptoms were itchiness around the lesion, fever, and lymphadenopathy; and patients did not have other systemic signs or symptoms of illness.

CASE 1

In July 2016, a 44-year-old woman, ethnically Azerbaijani, living in the rural area of Kvemo Kartli region sought medical attention for a painless lesion on her hand. She reported she was a housewife who milked cows and cleaned her own small farm. She did not recall any sores or lesions on her animals. She characterized the lesion as initially appearing as a pustule progressing to an ulcerated skin lesion over a period of approximately 2 weeks. When examined during the investigation, the lesion appeared to be a ragged ulceration with partial eschar located on the dorsolateral aspect of the left thumb base (Figure 2). An initial diagnosis of cutaneous anthrax was made by the health-care worker; however, no specific treatment was prescribed. A lesion swab was obtained and sent to the Richard Lugar Center for Public Health Research, where testing for anthrax was negative and the PPV generic real-time PCR test was positive.

TABLE 1
Demographic characteristics and risk factors for exposure to parapoxvirus infections in Georgia

Demographics			Risk factors*					
			Cleaning farms	Contact with animal products	Perform earthwork	Contact with animals	Cow milking	Animal with observed skin lesion
Gender	Female	56% (15)	7	5	3	9	14	6
	Male	44% (12)	10	3	2	7	5	6
Age group	10–19 years	7% (2)	2	1	0	0	0	1
	20–29 years	19% (5)	2	1	1	2	3	3
	30–39 years	26% (7)	5	1	1	4	5	3
	40–49 years	26% (7)	3	3	1	4	5	2
	50–59 years	15% (4)	3	2	2	4	4	3
	60–69 years	7% (2)	2	0	0	2	2	0
Ethnicity	Georgian	78% (21)	14	5	5	13	15	10
	Azerbaijani	18% (5)	2	3	0	2	3	1
	Armenian	4% (1)	1	0	0	1	1	1
Occupation	Farmer	15% (4)	4	0	1	3	2	2
	Housewife	48% (13)	6	3	2	8	13	6
	Pensioner	4% (1)	1	0	1	1	1	1
	Student/school boy	7% (2)	1	1	0	0	0	0
	Other	15% (4)	3	2	1	2	2	2
	Unemployed	11% (3)	2	2	0	2	1	1

* Risk factors were not mutually exclusive.

FIGURE 2. Black eschar 2 weeks after the onset on the left hand of a 44-year-old female with confirmed parapoxvirus infection. This figure appears in color at www.ajtmh.org.

CASE 2

In December 2016, a 29-year-old female, ethnically Azerbaijani, residing in the rural part of Kvemo Kartli region was referred to the hospital for evaluation of a painless ulceration on the dorsal aspect of the distal right index finger (Figure 3). She reported that she was a housewife who regularly milks cows but otherwise does not have contact with animals. She did not observe any lesions or sores on the animals. After the appearance of her ulceration, she visited a regional hospital for evaluation where anthrax was suspected and was referred to an infectious diseases hospital in Tbilisi. The patient did not receive any antiviral or antibiotic drugs. External consultation from NCDC was requested and testing for PPV was recommended. The PPV generic real-time PCR test was positive.

CASE 3

In October 2016, a 20-year-old male student, ethnically Georgian, residing in the rural area of the Imereti region presented to a hospital for evaluation of a pustule that developed on the proximal aspect of his distal right middle finger approximately 2 weeks after injuring his finger and breaking the skin on a sheep's tooth in the process of slaughtering the animal. The patient had not noticed any sign of a disease in the sheep and did not have contact with any other animals. The patient recalled purchasing the sheep in Kakheti region 3 days before he brought it to Imereti. He visited the doctor

FIGURE 3. Lesion 3 weeks after the onset on the right hand of a 29-year-old female with confirmed parapoxvirus infection. This figure appears in color at www.ajtmh.org.

the day following lesion development. No other symptoms were reported, and no antimicrobial therapy was used. A swab of the lesion was obtained the day after presenting to the hospital, and laboratory results were available in 4 days. Generic real-time PCR testing for PPV was positive.

CASE 4

In March 2016, a 29-year-old male, ethnically Georgian, from the rural area of Imereti region visited a local hospital with multiple pustules on both of his hands. He reported being involved in a number of farm-related activities, including milking cows, cleaning farms, assisting animals during labor, and performing earthwork. He also reported contact with an animal with obvious skin lesions (or sores), although it was otherwise healthy. The doctor advised the patient to watch the lesions and return for follow-up evaluation in several days. After 5 days, the lesions were still present and cutaneous anthrax was suspected. The doctor prescribed oral administration of ciprofloxacin and an injection of ceftriaxone for treatment. The patient was later hospitalized in another clinic, where NCDC's regional epidemiologist performed additional investigation and discovered that the patient had seen several ulcers on the udders of cows that he had been working with. Ulcer swabs were taken from the patient and sent to the referral laboratory for testing; *Bacillus anthracis* testing was negative and PPV was confirmed with generic real-time PCR. The patient recovered.

DISCUSSION

The risk factors and clinical details of PPV cases in this series provide helpful insight regarding the presentation of disease in Georgia while also lending supportive evidence for PPV surveillance and reporting. These cases clearly highlight the need for Georgian physicians to consider PPV infections in the differential diagnosis of cutaneous lesions in humans, particularly in the presence of known animal exposure. In this series, all cases reported exposure to cows or sheep. Interestingly, housewife was the most common occupational category for the reported cases. Among their frequent duties, housewives in Georgia are often involved in frequent and sustained farm-related activities, for example, milking and caring for farm animals and cleaning the farm, which characterize the principle behavioral and occupational risk factors for Cases 1 and 2. The males with PPV infection in this series had more varied occupations, but like those for housewives, cleaning farms and animal exposure were common exposure risks. Nontraditional exposures, such as meat processing or animal slaughter have been noted in other studies²³ and were seen in one case in this series, Case 3, which involved breaking the skin on a sheep's tooth in the process of slaughtering the animal.⁷

It is important to recognize the geographic distribution of PPV infections in humans and animals to alert clinicians to the possibility of disease, decrease the use of unnecessary antibiotics following misdiagnosis, and to better focus prevention efforts to more effectively prevent transmission of disease. The frequent misdiagnosis of PPV-related cutaneous lesions as anthrax generally results in the prescription of unneeded and ineffective antibiotics⁴ and is especially problematic in areas where antibiotic use is poorly regulated. The improper use antibiotics can contribute to the development of

resistance and is associated with treatment complications and increased health-care costs.²⁶ Case 4 is a classic example of a misdiagnosis followed by the unnecessary use of antibiotics and speaks directly to the need to better educate clinicians in Georgia about PPV and its recognition.

Parapoxvirus infections may result in decreased milk supply among dairy animals¹ and is, therefore, of economic importance to Georgia's agricultural sector. Prevention of transmission²⁷ of PPV infection to other animals may include quarantine of new animals, isolation of affected animals, and disinfection of fomites such as troughs or feeders. People caring for animals⁷ should consider wearing nonpermeable gloves during contact with animals that show any signs of skin lesions or damage to prevent acquisition of PPV infection.

Parapoxvirus infections have been documented in Turkey for years but were undetected and unreported in Georgia until poxvirus surveillance was established through the EIDSS and NCDC systems in 2016. It is likely that PPV was actually present in Georgia but went unrecognized, given the generally benign and self-limited nature of PPV disease and the fact that infected persons often do not seek medical attention. The introduction of PPV surveillance and testing in Georgia has raised awareness that poxviruses should be included in the differential diagnosis of cutaneous lesions in humans. A number of diseases, including cutaneous anthrax, leishmaniasis, and OPXVs,^{6,7} share some similar clinical characteristics and exposure risk factors, which make it more difficult to establish the etiology of disease without confirmatory laboratory testing. Cutaneous anthrax is regarded as an endemic disease in Georgia,¹⁷ with an incidence ranging between 1.0 and 3.5 per 100,000 over the past several years ($N = 42$ –143 cases). In addition, diagnostic testing and surveillance for anthrax has been in place since the 1940s in Georgia. Given their familiarity with anthrax, Georgian clinicians are generally much more likely to suspect anthrax as the etiology of skin lesions especially with a history of animal contact, as seen in this study.

Enhanced awareness and increased availability of poxvirus testing has improved the detection of disease in Georgia. Expansion of the NCDC surveillance system to include PPV was accompanied by provider education and improved access to PCR testing. Methods described by Zhao et al.²⁵ have proven to be a highly sensitive diagnostic tool, useful for screening and surveillance purposes. In this series, only PCR identification to the PPV genus was available; species identification is an objective for future investigations. In Georgia, educational campaigns were organized to assist health-care workers in identifying suspected PPV infections and in the use of proper diagnostic tools. This may have resulted in higher numbers of cases reported in regions where trainings were organized earlier (Imereti, Kvemo Kartli, and Shida Kartli) compared with others (Adjara and Mtskheta-Mtianeti). Educational campaigns for clinicians should continue to further improve surveillance for and detection of PPV. Expanded surveillance activities should be considered for neighboring countries to better characterize the prevalence of PPV infection in this region of the world.

We found a considerable lag between onset of symptoms and PPV diagnosis, generally about 2 weeks, which may have been a result of the severity and progression of lesions, availability of a health-care provider, distance to a clinic or hospital, rapidity of disease report by healthcare workers, and sampling and transportation timeliness for specimen from

hospital to referral laboratory, among others. We were unable to determine the relative contribution of each of these variables on diagnostic timeliness, but this requires further investigation to identify strengths and weaknesses of the current surveillance and reporting systems.

LIMITATIONS

This study has certain limitations. The cases are obtained from a surveillance system that relies on the medical doctors' ability to diagnose and report the disease. Although training on epidemiology, identification of clinical symptoms, sample collection, diagnosis, and prevention of poxviruses were initiated in the summer of 2015, specialists in certain regions were trained later than others, and those individuals might have been less proficient in identifying suspected PPV infections. Surveillance data may not reflect the true prevalence of the disease in different regions of the country. The limited clinical descriptions included in this series are based on information obtained from the EIDSS and were not extracted from medical records. The PCR testing was performed only to the level of PPV genus in these cases; future research should include speciation of virus to better understand disease distribution. Data on prevalence of PPV infections in animal populations were not available; however, establishment of PPV surveillance in the veterinary sector is in process; combining surveillance of PPV infection in animals and humans will further enhance the One Health approach.

CONCLUSION

This study presents the first epidemiologic description of PPV infections in the country of Georgia. Parapoxvirus infections occur throughout the country and should be considered in the evaluation of cutaneous disease in both humans and animals. These findings contribute to our understanding of the global distribution of PPV infections and can assist with future efforts to prevent and reduce the burden of disease, improve surveillance for poxvirus-related illness, and better protect human and animal health.

Received November 10, 2017. Accepted for publication February 26, 2018.

Published online April 9, 2018.

Acknowledgments: We appreciate the assistance of Abram L. Wagner, PhD, with providing the map image. The Centers for Disease Control and Prevention (CDC) provided technical support to the country of Georgia to set up these surveillance systems.

Financial support: This publication is sponsored by the U.S. government and Cooperative Biological Engagement Program with support from CRDF Global. The content of the information does not necessarily reflect the position or the policy of the federal government and no official endorsement should be inferred.

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