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https://doi.org/10.1016/j.jaad.2018.08.019

Possible long-term sequelae in hand, foot, and mouth disease caused by Coxsackievirus A6

To the Editor: We read with interest a paper disclosing the enterovirus (EV) types responsible for hand, foot, and mouth disease (HFMD) in Chinese children.[1] Among 2571 EV-positive cases, three quarters were attributed to 3 predominant types: Coxsackievirus (CV)-A16, CV-A6, and EV-A71. However, the report did not deal with EV-related atypical exanthems[2] nor with the possible long-term consequences of these infections.

We studied the clinical and virologic features of patients with skin/mucosal lesions seen at the Dermatology Department of the San Martino Hospital (Genoa, Italy) between November 2014 and March 2016. Clinical data and pictures of skin/mucosal lesions were acquired. To corroborate the diagnosis, blood was drawn for serology and polymerase chain reaction for viral genomes (all members of the EV genus[2] and other exanthem-inducing agents: cytomegalovirus, Epstein–Barr virus, human herpesviruses-6, -7, and -8, and parvovirus B19 [PVB19]). Fourteen cases with serology suggestive of recent enteroviral infection were selected.

Ten of the 14 cases had enterovirus RNA in plasma: sequencing identified the infecting pathogen as CV-A6. Cases 1 and 10 were also positive for PVB19. Cytomegalovirus, Epstein–Barr virus, and human herpesviruses-6, -7, and -8 could not be detected.

Investigated cases were: typical HFMD (1 case; petechial adult maculopapules or vesicles on the extensor surfaces of hands, feet, and oral mucosa), atypical HFMD (5 cases; absence of involvement of 1 typical site or involvement of adjacent sites, such as the face, scalp, and ankles), and atypical exanthems (4 cases; maculopapular eruption over the whole body). As seen in Table I, 9 cases had oral papulovesicles or petechiae, 5 cases had cutaneous erythematovesicles (on the hands and feet), 4 cases had maculopapules with petechiae, and 3 cases had erythematous papules on the trunk. Other affected body sites included the face, scalp, elbows, legs, and buttocks. Lesions were reported as burning/itchy. Two patients presenting with maculopapules on the buttocks were coinfected with PVB19. Cases 3 and 6 developed early complications—orchiepididymitis and onychomadesis, respectively. On average, clinical resolution occurred in 12 days.

The 10 patients were followed-up for 2 years. Clinical examinations highlighted conditions that may be considered sequelae of the initial infection (Table I): case 3 developed degenerative mitral valve disease and maintained low-level CV-A6 viremia, indicating that the virus had established low-level persistence in the host; cases 2, 8, and 10 developed persistent myalgia/arthralgia. Notably, case 2 (negative at the onset for antinuclear antibodies, antineutrophil cytoplasmic antibodies, and rheumatoid factor antibodies) developed symmetric polyarthritis with rheumatoid factor positivity and antibodies to cyclic citrullinated peptides. PVB19 was not detected in any cases.

The variable clinical expression at onset[3] and the development of changeable longstanding sequelae in patients infected by the same virus type could be linked to the unpredictable expression pattern of the multiple EV receptor types in different subjects.[4,5]

In closing, severe atypical HFMD may be followed by long-term sequelae. It is therefore important to recognize different HFMD forms and to obtain detailed virology reports. It is also important to use long-term follow-up programs to uncover the possible longstanding sequelae of this condition that is emerging in adults.

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Supported by Fondo Ateneo, Quota Competitiva, University of Milano Bicocca grant 2016-ATESP-0032 to Dr Broccolo, Italian Ministry of Health

Table I. Clinical presentation, viral determinations, and sequelae at the 2-year follow-up of adult patients with severe atypical had, foot, and mouth disease associated with Coxsackievirus type A6 viremia

	Clinical onset					Follow-up at 2 years		
				Plasma viremia			Plasma viremia	
Case no. (age years/sex)	Presentation to emergency department	Systemic symptoms	Pattern of lesions and involved body sites	CV-A6 RNA	PVB19 DNA	Clinical conditions	CV-A6 RNA	PVB19 DNA
1 (50/M)	Yes	Malaise, fever, arthralgia	EV (feet, hands, and scalp); MP (legs, buttocks); V (hard palate)	+	+	Idiopathic ventricular tachycardia	–	–
2 (35/F)	Yes	Malaise, fever, arthralgia	MP (trunk, hands, and feet); PE (hard palate)	+	–	Persistent myalgia/ arthralgia; SD	–	–
3 (18/M)	Yes; subsequent hospitalization	Malaise, fever, anorexia	EV (face, hands, scalp, legs, and forearms); MP (trunk); V (hard palate); bilateral orchiepididymitis	+	–	Mild DMDV (persistent low-level CV-A6 viremia)	+	–
4 (21/F)	Yes	Malaise, fever, arthralgia	MP (trunk, hands, and feet); M (hard palate); EP (elbows)	+	–	None	–	–
5 (51/M)	Yes; subsequent hospitalization	Malaise, high- fever, arthralgia, myalgia	EV (face, hands, scalp, legs, and hard palate)	+	–	Impaired glucose tolerance	–	–
6 (28/M)	Yes	Malaise, fever, anorexia	EV (face, scalp, hands, and hard palate); onychomadesis	+	–	None	–	–
7 (43/M)	Yes	Malaise, fever, anorexia	EV (face, neck, hands, feet, and hard palate)	+	–	None	–	–
8 (56/F)	Yes	Malaise, fever, arthralgia, anorexia	MP (hands, feet, and legs)	+	–	CFS; mild DMDV; persistent myalgia/ arthralgia	–	–
9 (52/M)	Yes	Malaise, fever, arthralgia	V (feet, hands, and hard palate)	+	–	Mild DADV/DMDV; SD	–	–
10 (33/F)	Yes	Malaise, fever, arthralgia	MP (trunk, hands, feet, and buttocks); EP (elbows); M (hard palate)	+	+	CFS; persistent myalgia/ arthralgia; SD	–	–

CFS, Chronic fatigue syndrome; *CV-A6*, Coxsackievirus type A6; *DADV*, degenerative aortic valve disease; *DMDV*, degenerative mitral valve disease; *EP*, erythematous plaques; *EV*, erythematovesicular; *M*, macular; *MP*, maculopapular; *P*, papular; *PE*, petechial; *PVB19*, parvovirus B19; *SD*, sleep disorder; *V*, vesicular; *VP*, vesiculopustular.
High fever is a temperature ≥38°C (≥100.4°F); fever is a temperature 37-38°C (98.6-100.4°F).

grant PE-2013-02357094 to Dr Toniolo, and The Juvenile Diabetes Research Foundation and Network for Pancreatic Organ Donors with Diabetes grant 25-2012-770 to Dr Toniolo. The study was conducted in collaboration with the Centro Linceo Beniamino Segre, Accademia dei Lincei, Rome, Italy.

Conflicts of interest: None disclosed.

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https://doi.org/10.1016/j.jaad.2018.08.034

Prognostic value of the Breslow:diameter ratio in cutaneous melanoma

To the Editor: The most frequently used staging system in melanoma is based on the TNM classification, which includes the variables for tumor thickness, lymphatic spreading, and the presence of distant metastasis and ulceration. The thickness of the primary tumor is assessed by the Breslow index, which influences the T stage; an increase in the Breslow index is directly associated with a decrease in overall survival and is the most decisive factor in this regard.[1,2] The diameter of a melanoma is not always related to its increase in depth, which brings into question whether a proportion that takes into

Table I. General characteristics of the series

Characteristic	Value
Age, y, n = 306, n ± SD (range)	52.3 ± 15.6 (8-85)
Sex, n = 306	
Male	142 (46.4)
Female	164 (53.6)
Diagnosis, n = 306	
Superficial spreading melanoma	219 (71.6)
Nodular melanoma	68 (22.2)
Acral lentiginous melanoma	14 (4.6)
Lentigo maligna melanoma	5 (1.6)
Location, n = 306	
Head and neck	23 (7.5)
Lower limb	93 (30.4)
Trunk	150 (49.0)
Upper limb	40 (13.1)
Diameter, mm, n = 306, n ± SD (range)	12.8 ± 7.8 (6-60)
Breslow index, n = 306, n ± SD (range)	2.35 ± 2.40 (0.17-23.00)
BDR, n = 306, n ± SD (range)	0.21 ± 0.23 (0.01-2.99)
Clark level, n = 298	
II	56 (18.8)
III	130 (43.6)
IV	93 (31.2)
V	19 (6.4)
TNM stage, n = 306	
I	145 (47.4)
II	91 (29.7)
III	70 (22.9)
Ulceration, n = 265	75 (28.3)
Regression, n = 256	73 (24.6)
Inflammatory infiltrate, n = 256	
No	39 (15.2)
Mild	106 (41.4)
Moderate	79 (30.9)
Severe	32 (12.5)
Lymphovascular invasion, n = 191	39 (20.4)
Satelitosis, n = 53	4 (7.5)
Mitotic rate, n = 139	
<1	16 (11.5)
≥1	123 (88.5)
<2	57 (41.0)
≥2	82 (59.0)
Previous excision, n = 306	273 (89.2)
No. lymphatic drainages, n = 306	
1	240 (78.4)
2	62 (20.2)
≥3	4 (1.3)
Surgical technique, n = 306	
Margins + plasty	4 (1.3)
Exeresis + graft	70 (22.9)
Margins	226 (73.9)
SNB only	6 (2.0)

Continued

You can get hand, foot, and mouth disease by. Contact with respiratory droplets containing virus particles after a sick person coughs or sneezes. Touching an infected person or making other close contact, like kissing, hugging, or sharing cups or eating utensils. Touching an infected personâ€™s feces, such as changing diapers, then touching your eyes, nose, or mouth. Touching objects and surfaces that have the virus on them, like doorknobs or toys, then touching your eyes, nose, or mouth.Â Coxsackievirus A16 is typically the most common cause of hand, foot, and mouth disease in the United States. Other coxsackieviruses can also cause the illness. Coxsackievirus A6 can also cause HFMD and the symptoms may be more severe. Background: Hand, foot, and mouth disease (HFMD) represents a substantial disease burden in the Western Pacific region. We investigated the spectrum of causative enteroviruses of HFMD, and evaluated different clinical samples' diagnostic yield for enteroviruses. Methods: We enrolled pediatric patients hospitalized for HFMD among six hospitals in Anhua County, Hunan Province, China between October 2013 and September 2016. Throat swabs and stool samples (or rectal swabs) were collected to detect the enterovirus serotypes by real time RT-PCR or nested PCR. Results: Among the 2,836 patients only one developed severe illness. Importance: Hand-foot-mouth disease (HFMD) is an acute, self-limited, highly contagious viral illness that commonly affects children younger than 5 years. It is most typically caused by enterovirus 71 or coxsackievirus A16 and results in asymptomatic infection or mild disease. Immunocompetent adults are rarely affected. Recently, there have been increasing reports of a more severe form of HFMD associated with fevers, joint pains, and widespread painful eruptions. Some of these patients required hospitalization for supportive care. These severe cases were most commonly caused by coxsackievirus A6. Outbreak of hand, foot and mouth disease/herpangina associated with coxsackievirus A6 and A10 infections in 2010, France: a large citywide, prospective observational study. Clin Microbiol Infect 2012; 18: E110â€“118. 19. Lu J, Zeng H, Zheng H, Yi L, Guo X, et al.Â Coxsackievirus A6 and enterovirus 71 causing hand, foot and mouth disease in Cuba, 2011â€“2013. Arch Virol 2014; 159: 2451â€“2455. 24. Hayman R, Shepherd M, Tarring C, Best E. Outbreak of vari-ant hand-foot-and-mouth disease caused by coxsackievirus A6 in Auckland, New Zealand. J Paediatr Child Health 2014; 50: 751â€“755. 25. Sinclair C, Gaunt E, Simmonds P, Broomfield D, Nwafor N, et al.