

3. Lee AN, Werth VP. Activation of autoimmunity following use of immunostimulatory herbal supplements. *Arch Dermatol*. 2004;140:723-727.
4. Werth VP, Callen JP, Ang G, Sullivan KE. Associations of tumor necrosis factor alpha and HLA polymorphisms with adult dermatomyositis: implications for a unique pathogenesis. *J Invest Dermatol*. 2002;119:617-620.
5. Alves P, Bashir M, Wysocka M, Zeidi M, Feng R, Werth VP. Quinacrine suppresses tumor necrosis factor- α and interferon- α in dermatomyositis and cutaneous lupus erythematosus. *J Invest Dermatol Symp Proc*. 2017;18:S57-S63.

<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 exanthems² 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 genus² 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 coinfecting 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/arthritis. 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 onset³ 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.

Francesco Broccolo, MD, BSc,^a Francesco Drago, MD,^b Giulia Ciccarese, MD,^b Angelo Genoni, BSc,^c Alice Porro, MD,^b Aurora Parodi, MD,^b Konstantin Chumakov, PhD,^d and Antonio Toniolo, MD^c

Department of Medicine and Surgery,^a School of Medicine, University of Milano-Bicocca, Monza; DISSAL Section of Dermatology,^b University of Genoa and Policlinico San Martino, Genoa; Medical Microbiology,^c Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy; and the Office for Vaccines Research and Review,^d Food and Drug Administration Center for Biologics Evaluation and Research, Silver Spring, Maryland

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 hand, foot, and mouth disease associated with Coxsackievirus type A6 viremia

Case no. (age years/sex)	Clinical onset				Follow-up at 2 years			
	Presentation to emergency department	Systemic symptoms	Pattern of lesions and involved body sites	Plasma viremia		Clinical conditions	Plasma viremia	
				CV-A6 RNA	PVB19 DNA		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 $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$); fever is a temperature $37\text{--}38^{\circ}\text{C}$ ($98.6\text{--}100.4^{\circ}\text{F}$).

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.

Drs Broccolo and Drago contributed equally to this work.

Correspondence to: Francesco Broccolo, MD, BSc, Department of Medicine and Surgery, School of Medicine, University of Milano-Bicocca, Via Cadore 38, Monza 20052, Italy.

E-mail: francesco.broccolo@unimib.it

REFERENCES

1. Gao L, Zou G, Liao Q, et al. Spectrum of enterovirus serotypes causing uncomplicated hand, foot, and mouth disease and enteroviral diagnostic yield of different clinical samples. *Clin Infect Dis*. 2018. <https://doi.org/10.1093/cid/ciy341>. [e-pub ahead of print]. Accessed October, 2018.
2. Drago F, Ciccarese G, Gasparini G, et al. Contemporary infectious exanthems: an update. *Future Microbiol*. 2017;12:171-193.
3. Drago F, Ciccarese G, Broccolo F, Rebora A, Parodi A. Atypical hand, foot, and mouth disease in adults. *J Am Acad Dermatol*. 2017;77:e51-e56.
4. Baggen J, Jan Thibaut H, Strating JRP, van Kuppeveld FJM. The life cycle of non-polio enteroviruses and how to target it. *Nat Rev Microbiol*. 2018;16:368-381.
5. Staring J, van den Hengel LG, Raaben M, Blomen VA, Carette JE, Brummelkamp TR. KREMEN1 is a host entry receptor for a major group of enteroviruses. *Cell Host Microbe*. 2018;23:636-643.e5.

<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 \pm SD (range)	52.3 \pm 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 \pm SD (range)	12.8 \pm 7.8 (6-60)
Breslow index, n = 306, n \pm SD (range)	2.35 \pm 2.40 (0.17-23.00)
BDR, n = 306, n \pm SD (range)	0.21 \pm 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)
Satellitosis, 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