Montrouge, 17-04-2019

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Varicella complicated by necrotizing soft tissue infection in childhood: an argument for systematic childhood varicella vaccination in France?

published in:
European Journal of Dermatology, 2019, Volume 29, Numéro 1

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doi:10.1684/ejd.2018.3441

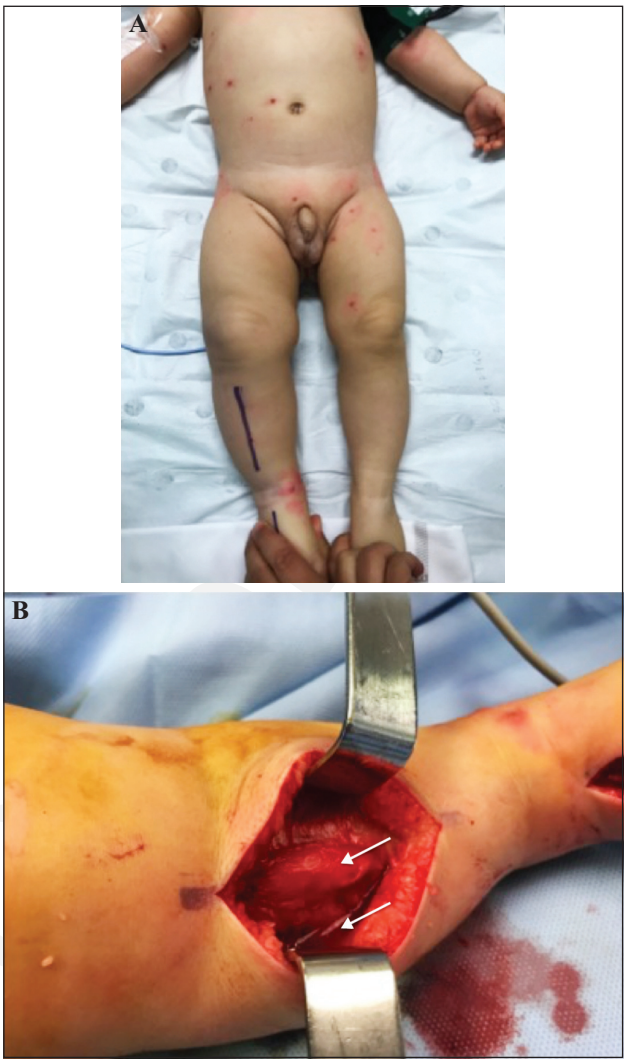

Figure 1. A) Preoperative image of patient 3 showing an oedematous right leg without erythema or skin necrosis; note the increased diameter of the whole right lower limb. **B)** Intraoperative image of patient 3 showing the infiltrated/swelling aspect of the muscle fascia and subcutaneous tissue (white arrow) without superficial skin lesions; note the muscle hernia through the fascia incision (white arrow).

Varicella complicated by necrotizing soft tissue infection in childhood: an argument for systematic childhood varicella vaccination in France?

Necrotizing soft tissue infection (NSTI) is a rare but severe and rapidly spreading infection leading to potential mortality and devastating morbidity in the paediatric population. Streptococci, staphylococci, and polymicrobial infections are classically implicated in patients with NSTI. Optimal management involves immediate appropriate antimicrobial therapy and debridement surgery. Any delay leads to an increased riek of mortality especially as the clinical presentation is unclear with no real pathognomonic clinical signs [1, 2].

The cases of three male children, aged one, five and six years old, affected by NSTI and varicella over a period of three months are presented. The patients were admitted to the emergency department due to NSTI at the University Hospital of Clermont-Ferrand, in France, between April and July 2017. Two of them (patients 2 and 3) belonged to the same family. The three patients did not have any comorbidities and all vaccines were up to date. At admission, all patients presented with a toxic appearance of the skin (with decreased sensitivity and poor peripheral perfusion) during reappearance of fever. The lower limb (patients 1 and 3) (*figure 1A*) and trunk (patient 2) were affected. Local

examination revealed oedema, induration, pain out of proportion, and functional impairment. The symptoms appeared with a delay of one to five days from the beginning of signs of varicella infection. The classic features of skin infection, such as erythema and local hyperthermia, were not present in any of the patients making the diagnosis of NSTI difficult initially (*supplementary table 1*).

The timeliness of clinical NSTI diagnosis impacts prognosis, and appropriate treatment without delay leads to better outcomes [1]. Children frequently lack pathognomonic clinical features or a toxic appearance of the skin, but some clinical signs such as oedema, an increased diameter of limbs, and reappearance of fever or pain out of proportion should be seriously considered within the context of varicella infection. Delayed erythema or apparition of skin necrosis may be due to NSTI initially affecting subcutaneous and muscle fascia.

Unlike adults, the laboratory risk factor, essentially based on biological markers, such as CRP, haemoglobin and leukocyte count, is not validated in children, however, CRP and creatinine kinase appear to be early non-specific elevated biological markers for NSTI in the paediatric population [2, 3].

Varicella was diagnosed based on clinical symptoms in all patients and confirmed by PCR for VZV (multiplex HSV 1 and 2 – VZV PCR). The diagnosis of NSTI was clinically suspected and then confirmed by early surgery (*figure 1B*) and histological examination of intraoperative biopsies. NSTI was defined as a soft tissue infection characterized by necrosis of subcutaneous tissue [1]. Bacterial analysis (including emm typing, genome analysis, and super antigen profiling) was performed using surgical samples [4]. The same group A β-haemolytic *Streptococcus* (GAS) bacteria with the same determinant of toxic virulence (emm 12.37, SpeB, SmeZ) was found in patients 2 and 3, highlighting an intrafamilial context of contagion. Imöhl *et al*. identified varicella as a risk factor for GAS infections with certain aggressive emm types, including emm type 12 [5].

In France, GAS and *Staphylococcus aureus* are the usual causative organisms involved in NSTI [2, 6]. The frequency of polymicrobial infections and the delay associated with tissue and blood cultures justify prompt initiation of empiric antibiotics in combination with amoxicillin and clindamycin [2, 6, 7]. This combination is effective against streptococcal, staphylococcal, *Bacteroides*, and Gram-negative species. Clindamycin plays an important role with its anaerobic and major antitoxic effects [2, 8, 9]. Initiation of antibiotics must not delay surgical treatment, although some doubt still remains regarding the occurrence of varicella co-infection in suspected cases of NSTI and a short time interval between the first physical examination and debridement surgery must be the incontrovertible rule [1, 2].

Thankfully, the occurrence of this disease is rare in children but can be encountered in patients with chronic disease, recent surgery, trauma, or varicella [2]. Varicella complicated by NSTI was not uncommon before the varicella vaccine era, but has disappeared with the near elimination of varicella in the United States, explicating the increasing age of patients with NSTI in the paediatric population, with a median age of 10 years old [6, 10]. In France, childhood varicella vaccination is not recommended from a public health perspective but concerns only teenagers aged 12 or more with no past medical history of varicella. A modification of this vaccination programme should therefore be discussed regarding these severe complications that are most of the time difficult to diagnose. ■

Disclosure. *Financial support: none. Conflicts of interest: none.*

Supplementary data

Supplementary data (Table S1) associated with this article can be found, in the online version, at doi:10.1684/ejd.2018.3462.

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doi:10.1684/ejd.2018.3462

Coexistence of anti-topoisomerase I and anti-RNA polymerase III antibody in a patient with overlap syndrome

A 27-year-old Japanese woman complained of dry eyes and mouth, increased hair loss, scattered erythema on the face, and Raynaud's phenomenon (*figure 1A*). The patient was diagnosed with systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) based on the findings of clinical, serological, and pathological examinations, including interface dermatitis in both the interfollicular epidermis and follicular epithelium, mucin deposition in the dermis, particularly around hair follicles, and cell infiltrates around sweat glands (*figure 1B-E*). Screening for autoantibodies against nuclear proteins (x320; HOMO+SP, CYTO+: the titre and pattern were consistent throughout the course), DNA (18 IU/mL), ssDNA (168 AU/mL), Sm (×1), SS-A (×16), and SS-B (×8) was positive. However, screening for autoantibodies against dsDNA, ANCA, antiphospholipid syndrome- and dermatomyositis-related disease was negative. Oral administration of prednisolone (PSL) at 20 mg/day was initiated. One year later while on PSL at 6 mg/day, the patient complained of arthralgia. The levels of matrix metalloproteinase-3 (286.9 ng/mL) were slightly increased. Serum rheumatoid factor was negative, but anti-cyclic citrullinated peptide (CCP) antibody (Ab) was positive (9.3 U/mL). Bone erosion and synovitis of the finger and knee joints were detected on X-ray and ultrasound, respectively, therefore, the patient was diagnosed with early rheumatoid arthritis (RA). Two years later, she

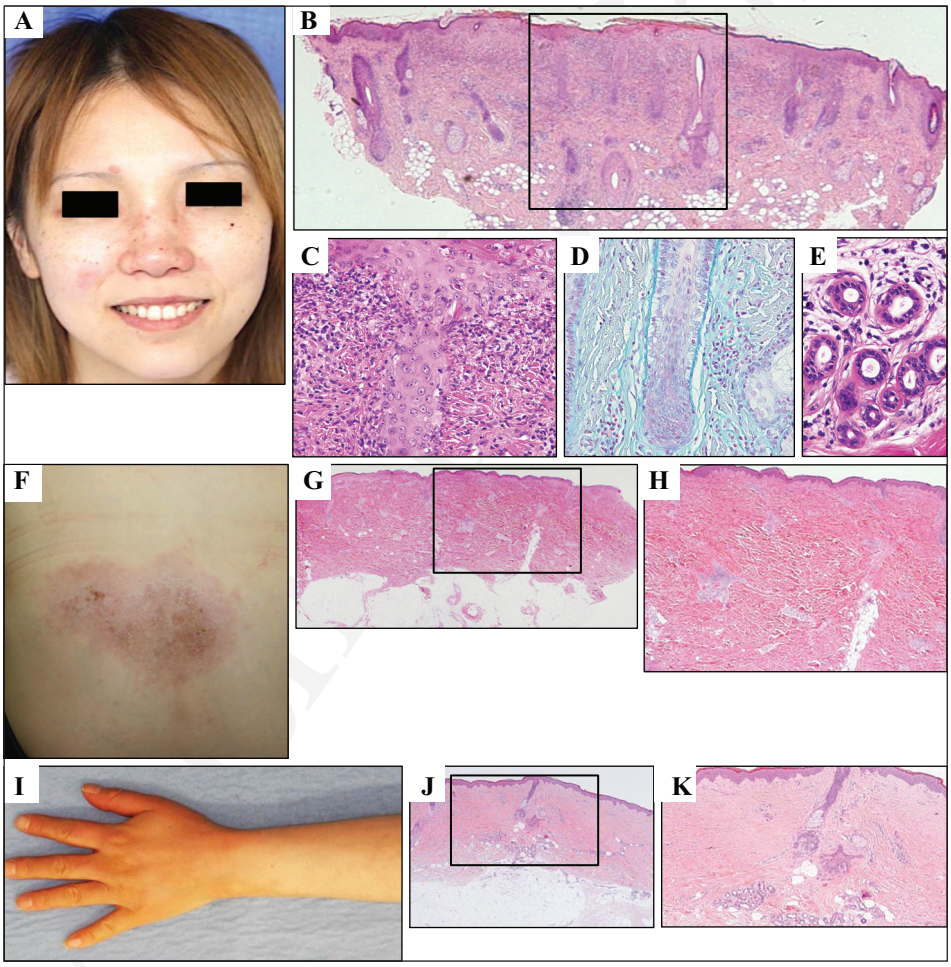

Figure 1. **A**) Clinical aspect of the patient. **B-E**) Histopathology of erythema of the patient's forehead, showing: (**B**) scanning image of erythema (haematoxylin-eosin [H&E] staining; ×40); (**C**) interface dermatitis in both the interfollicular epidermis and follicular epithelium (H&E staining; ×200); (**D**) mucin deposition in the dermis, particularly around hair follicles (alcian blue staining; ×200); and (**E**) cell infiltrates around sweat glands (H&E staining; ×200). **F**) A reddish oval patch on the back. **G**, **H**) Histopathology of the oval patch of the back shows thickened and hyalinized collagen (H&E staining; [**G**] ×40, [**H**]: ×100). **I**) Sclerosis of the patient's fingers and forearms. **J**, **K**) Histopathology of sclerotic skin of the patient's forearm shows thickened and hyalinized collagen (H&E staining; [**J**] ×40, [**K**] ×100).