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Commentary

Single organ cutaneous vasculitis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data

Giovanna Zanoni [a,*], Giampiero Girolomoni [b], Caterina Bonetto [c], Francesco Trotta [c], Peter Häusermann [d], Roberta Opri [a], Jan Bonhoeffer [e,f]
The Brighton Collaboration Single Organ Cutaneous Vasculitis Working Group [1]

[a] Immunology Unit, University Hospital, Verona, Italy
[b] Department of Medicine, University of Verona, Verona, Italy
[c] Italian Medicines Agency (AIFA), Rome, Italy
[d] University Hospital Basel, Basel, Switzerland
[e] University Basel Children's Hospital, Basel, Switzerland
[f] Brighton Collaboration Foundation, Basel, Switzerland

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1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for single organ cutaneous vasculitis as an adverse event following immunization

Vasculitides are a group of heterogeneous conditions characterized by inflammation of blood vessel wall, which can occur in any organ system. Cutaneous involvement occurs almost exclusively with vasculitis of small and medium-sized vessels [1]. Cutaneous vasculitis (CV) may be: (a) a single organ disease limited to the skin, (b) primary CV with secondary systemic involvement, or (c) a cutaneous manifestation of systemic vasculitis [1].

Several classifications and definitions have been proposed for vasculitides, for example those published by the American College of Rheumatology and the Chapel Hill Consensus Conference (CHCC), but they all have various limitations [2–4]. The proliferation of names for CV is principally due to the fact that various disorders can be associated with small-vessel vasculitis of the skin: sometimes it is only cutaneous and in other cases there can be other organ involvement [5].

In 1952, upon the first classification, the term "hypersensitivity vasculitis" (HV) was coined to distinguish forms of necrotizing arteritis of small vessels from polyarteritis nodosa (PAN), which involved larger vessels. HV derives its name from animal models of vasculitis induced by horse serum or drug administration to cause hypersensitivity reactions [5]. Subsequently, the term has been refined to denote small vessel vasculitis confined mainly to the skin and not associated with any other primary vasculitis (i.e. Henoch-Schoenlein purpura, granulomatosis with polyangiitis or cryoglobulinemia). The 1994 CHCC proposed an alternative term for HV - "cutaneous leukocytoclastic angiitis" because of the frequent failure to identify a precipitant factor for hypersensitivity

Abbreviations: AHEI, acute haemorrhagic edema of infancy; ANCA, anti-neutrophil cytoplasmic antibodies; BCG, Bacillus Calmette-Guerin; CHCC, Chapel Hill Consensus conference; CSVV, cutaneous small vessel vasculitis; CV, cutaneous vasculitis; C3, C4, C1q, serum complement factors 3, 4, 1q; HA, Hepatitis A; HB, Hepatitis B; HPV, human papilloma virus; HSP, Henoch-Schoenlein purpura; HUV, hypocomplementemic urticarial vasculitis; HV, hypersensitivity vasculitis; IC, immune complexes; MMR, measles, mumps, rubella; PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus; SOCV, single organ cutaneous vasculitis; UV, urticarial vasculitis.

* Corresponding author.
E-mail address: contact@brightoncollaboration.org (G. Zanoni).
[1] Brighton Collaboration homepage: http://www.brightoncollaboration.org.

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reaction. This term was also problematic because histological features were not always consistent with this clinical phenotype [5]. The more comprehensive definition of cutaneous small vessel vasculitis (CSVV), which includes clinical and histological features of HV and leukocytoclastic vasculitis irrespective of a possible triggering factor is also used. More recently, the 2012 revised CHCC nomenclature recommended that for single organ vasculitis, which is applied to vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis, the involved organ and vessel type should be included in the name (e.g. cutaneous small vessel vasculitis) [4]. Therefore, for this case definition we adopted the term single organ cutaneous vasculitis (SOCV), which refers to small vessel vasculitis of the skin where systemic involvement has been excluded.

1.1.1. Subtypes of single organ cutaneous vasculitis

CSVV is the most common type of vasculitis, and primarily affects cutaneous post-capillary venules of the dermis [6]. In most cases, it is histologically characterized by leukocytoclastic vasculitis, but lymphocytic vasculitis has been described too. The term CSVV is generally reserved for small vessel vasculitis of the skin without medium-sized vessel involvement, regardless of the clinical severity of the skin disease or the underlying etiology. CSVV is often idiopathic in nature, but may be secondary to an underlying cause such as an infection or medication. Extracutaneous involvement may occur but it is uncommon and usually mild [1].

In the group of CSVV a well-characterized form is urticarial vasculitis (UV), a small vessel vasculitis with predominant skin involvement manifesting with urticarial lesions [7,8]. UV consists of persistent urticarial lesions (beyond 24–36 h) showing the histopathological features of leukocytoclastic vasculitis [1]. Lesions consist of erythematous, indurated wheals, with or without angioedema, particularly on the trunk and lower extremities. Lesions are associated with burning and pain rather than pruritus and leave post-inflammatory hyperpigmentation and bruising. Although UV is most often idiopathic, it can be associated with autoimmune connective tissue diseases, infections, medications and haematologic malignancies [8]. The most important prognostic feature is the presence or absence of hypocomplementemia. More severely affected patients often are those exhibiting hypocomplementemia. The typical age group involves young to middle-aged women [9]. Seventy to eighty percent of cases of UV have normal complement levels in blood samples [1]. These patients tend to have a skin-limited disease, whereas those with decreased complement levels are more likely to have systemic manifestations [1]. About 80–90% of patients with hypocomplementemic urticarial vasculitis (HUV) may meet the criteria for diagnosis of systemic lupus erythematosus (SLE), or Sjogren syndrome or cryoglobulinemia [5].

Another manifestation of CSVV is acute haemorrhagic edema of infancy (AHEI), also known as Finkelstein's disease, a benign cutaneous leukocytoclastic vasculitis affecting children aged 4 months to 2 years. It was considered to be a cutaneous variant of Henoch-Schöenlein Purpura (HSP); however, unlike HSP, clinical manifestations, lesion location and histology of skin lesions differ [10].

In this document other subtypes of CSVV associated with systemic involvement (i.e. anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, cryoglobulinemia) are not discussed. Polyarteritis nodosa (PAN) can rarely manifest as SOCV. However, as it is characterized by specific clinical and histological features due to the involvement of medium-size vessels, it is envisioned to be defined separately.

1.1.2. Epidemiology

CV occurs in all age groups (mean age in adults, 47 years; mean age in children, 7 years), has a slight female predominance, and is much more common in adults than in children (about 90% of cases in adults and 10% in children) [1]. The incidence of biopsy-proven CV of all types is 15–60 patients per million per year. Studies from Spain have reported an annual incidence of 30 cases of HV per million adults per year [11]. Carlson et al. [12] reported that about 40% of patients presented CV associated with infections or drugs, 18% with connective tissue diseases or other systemic disorders including malignancies, 10% had HSP, and 4% primary systemic vasculitides; about 40% of cases were classified as idiopathic with an incidence (median rate) ranging from 15.4 to 29.7/1,000,000. Children who present with signs of cutaneous vasculitis, most frequently have HSP (88%), but also granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis) and PAN [12].

HUV may occur with or without systemic manifestations, while normo-complementemic UV (NUV) usually manifests without systemic involvement [13]. NUV has slight female predominance, whereas HUV is seen almost exclusively in female patients, with a peak of incidence in their forties for both forms. UV is a rare condition in children [8]; only a few paediatric cases have been reported, which are characterized by more severe renal disease than in adults [11]. The disease follows a chronic-relapsing, but limited term, course with an average duration of three years [13]. AHEI is a rare small-vessel vasculitis; there have been approximately 300 cases reported in the literature [10]. However, these figures do not reflect the actual incidence, as most AHEI cases are not reported. Epidemiological data on this rare manifestation are lacking, probably also because in the past it was considered a variant of HSP.

1.1.3. Etiology and pathogenesis

Disease-inducing or promoting factors are not known for more than half of cases of CSVV and are currently classified as "idiopathic". The remainder are most often either post-infectious or drug-induced [6]. Although non-immunologic factors such as direct infection of endothelial cells can cause vasculitis, most lesions are mediated by immunopathogenetic mechanisms. These mechanisms can be classified into Gell and Coombs' four types of hypersensitivity reactions [12]. However, the majority of cutaneous lesions are likely due to immune complexes (IC) deposition/type III hypersensitivity reactions [12]. IC deposition in postcapillary venules activates complement, which, in turn, induces mast cell degranulation and neutrophil chemotaxis. Neutrophils release proteolytic enzymes and free oxygen radicals, leading to damage of the vessel wall [1]. Increased adhesion between inflammatory cells and endothelium due to enhanced expression of adhesion molecules also plays a role in the pathogenesis of CV [1]. Although ANCA production is an important pathogenetic feature of some types of vasculitides with cutaneous manifestations, it is a typical marker of systemic involvement. Thus it will not be further discussed here.

Small vessel vasculitis can also be associated with connective tissue diseases and it may be a heralding sign of such diseases, particularly SLE. Vasculitis due to underlying connective tissue disease may be associated with more significant involvement of other organ systems [6]. Furthermore, a series of various other conditions can be associated with cutaneous vasculitic disease. This includes chronic infections, hematologic diseases, malignancies, physical exercise, or exposure to physical stimuli [13]. The pathogenesis of UV is thought to be mediated by a type III hypersensitivity reaction, with the formation of IC which deposit at the vessel walls and lead to complement activation [13]. In AEHI, there is almost always a preceding trigger, more frequently an upper viral