Commentary

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

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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]. 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].

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Abbreviations: AHEI, acute haemorrhagic edema of infancy; ANCA, antineutrophil 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; HEP, 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.

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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. 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-Schönlein 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 AHEI, there is almost always a preceding trigger, more frequently an upper viral
or bacterial respiratory tract infection, and less commonly medications or immunizations [10]. Once a patient has been diagnosed with CV, an attempt must be made to determine the etiology as its withdrawal (drug) or treatment (infection) may lead to resolution [12].

1.1.4. Clinical features
CSVV typically presents 7–14 days after exposure to a triggering agent with a single crop of lesions consisting of palpable purpura (hemorrhagic papules), erythematous papules, urticarial lesions, vesicles and hemorrhagic vesicles [14]. More rarely skin necrosis or pustules can be observed. CSVV favours dependent areas, as well as areas affected by trauma or under tight-fitting clothing. The lesions are usually asymptomatic, or associated with burning, pain or pruritus. Residual post-inflammatory hyperpigmentation may persist for months after the primary process resolves [1]. Manifestations typical of medium vessel vasculitis, such as subcutaneous nodules, livedo reticularis, retiform purpura, larger hemorrhagic bullae and ulceration are usually absent [6]. Constitutional symptoms, such as fever, myalgias, may accompanies flares of CSVV. Systemic symptoms develop in 5–25% of patients; in general, signs and symptoms of gastrointestinal, renal or neurologic involvement should increase the clinical suspicion for a systemic vasculitis. In one study, the presence of paresthesias or fever and the absence of painful lesions were identified as risk factors for an associated systemic disease [15]. About 90% of patients will have spontaneous resolution of cutaneous lesions within several weeks or a few months, while another 10% will have chronic or recurrent disease at intervals of months to years [16]. UV presents with urticarial lesions; the wheals are long-lasting and painful, and usually resolve with bruising or hyperpigmentation [13]. AHEI is characterized by a classic triad of symptoms: low grade fever, edema, a typical purpuric rash involving the face, ears, and extremities. The picture may be dramatic for the sudden onset of the lesions, but it has a good prognosis, with most cases being self-limited and resolving within 1–3 weeks without complications [10].

A careful history and review of other organ systems is essential for separating patients with skin-limited vasculitis from those with more significant systemic involvement or an underlying disease. Because such patients may have identical physical findings on initial presentation, the clinical history is of paramount importance to recognize extra cutaneous manifestations [6]. In most cases of CSVV, significant systemic manifestations are unlikely. After thorough history, review of systems and physical examination, a systematic and targeted laboratory workup should proceed to confirm a SOCV. No standard protocol for this workup exists, but screening tests should aim at elucidate the underlying cause and extent of organ involvement and should be guided by clinical signs and symptoms [6].

1.1.5. Cutaneous vasculitis as an adverse event following immunization (AEFI)
The literature search identified 16 publications (13 case reports, 1 case series and 2 reviews) hypothesizing a potential association between immunization induction or promotion of CV (see Table 1) [17–32]. We intended the term SOCV as comprising: leukocytoclasic vasculitis, lymphocytic vasculitis, UV, CV. Seven articles referred to influenza vaccination, two to hepatitis A (HA) and hepatitis B (HB) vaccination, two to Bacillus Calmette-Guerin (BCG) vaccination and one to anthrax, Human Papillomavirus Vaccine (HPV), measles-mumps-rubella (MMR) and pneumococcal vaccination, respectively. None of them applied a case definition for the diagnosis. In thirteen articles authors considered the association as possible or likely. Liu et al. and Hughes et al. [25,27] did not specify if they found an association, and Drucker et al. [20] rejected an association of lymphocytic vasculitis in a 26-year-old female following HB vaccination. Twelve papers (75%) reported the skin biopsy for histological confirmation.

Famularo [21], Ulm [30], and Walker [31] described leukocytoclasic vasculitis after influenza vaccination in people aged >60 years. All three authors agreed to consider that the mechanism of vasculitis associated with influenza vaccination is uncertain; however, experience with other vaccines suggests it may be related to hypersensitivity, or may involve the trigger of underlying inflammatory or autoimmune disorders [21]. In 2003 Lyngekran [32] described a 29-year-old female smoker, who developed burning pain and bluish discoloration of the tips of several fingers and toes two weeks after influenza vaccination. The author concluded that the proof of a causal relationship was not available.

There is one case of a 17-year-old girl after immunization with pandemic influenza A H1N1 vaccine [27]. Three days after vaccination she developed painful eruptions with symmetric erythematous vesicular papules, located predominantly on her trunk, arms and thighs. The lesions resolved completely without scarring in two weeks. Tavadiya et al. [29] described four cases of leukocytoclasic vasculitis following influenza vaccination. These four patients, who were all elderly, presented with CV but they all had abnormal urinalysis suggestive of associated renal involvement. The authors affirmed that they could not establish a causal association beyond the temporal association within 1–2 weeks following immunization. Authors concluded that the mechanism by which influenza vaccines cause vessel damage is likely to be due to abnormal immunological activation. A review by Hehn et al. [24] focused on influenza vaccination and subsequent skin diseases in subjects from 5 to 92 years of age. In a second part, the paper also reports 29 cases from the German spontaneous reporting system. The authors concluded that vasculitis has been documented to be associated with influenza vaccination [24].

Of the 2 articles concerning hepatitis, one referred to HB [20], mentioned above, and one to HA [17] that described a previously healthy 24-year-old man who received HA vaccine (Havrix®) for the first time and developed fever (temperature, 38.5 °C), arthralgia, and a petchial purpuric rash on the lower extremities 9 days later. Of the two articles about BCG vaccination, one is a report of a single case and one is a review. The review by Bellot in 2005 [18] focused on the cutaneous complications of BCG vaccination. Ghatatura [23] described a case of a 12-year-old girl with ulcerating vasculitis. The two authors [18,23] concluded that cutaneous complications of BCG vaccination are rare.

Muniz [26] reported a case of a previously healthy 53-year-old male with lymphocytic vasculitis temporally associated with the anthrax vaccine. He presented painful rash localized to the lower extremities and after his fourth anthrax vaccination received 11 days before. The author concluded that a rare, previously unknown adverse effect, such as lymphocytic vasculitis, may occur.

In a poster in 2011 Chaudhari reported a case of an healthy 13-year-old girl with a possible UV after HPV vaccination with Gardasil® [19]. The author concluded that this reaction was a rare, potential complication to the HPV vaccine and further elucidation of a causal vasculitis-inducing component in Gardasil® could be important.

Sedaghat [28] reported a case of a previous healthy 17-year-old girl that developed generalized maculopapular skin rash after MMR vaccination. The author concluded that a dermal vasculitis may occur after MMR vaccination.

Fox [22] reported a case of a relatively healthy 57-year-old man who developed maculopapular rash initially surrounded the injection site and subsequently spread. The authors concluded that “minor reactions to pneumococcal vaccination are common”.

In addition we also considered three reviews referring to multiple vaccines, two about AHEI [33,34] and one on CV in children [10]. AHEI is an uncommon leukocytoclasic small-vessel vasculitis
of young children. Fiore et al. [33,34] between May 2007 and April 2008 analysed the distribution of the 294 children with AHEI between 2 and 60 months (median 11 months) of age and was almost identical in boys (67% of the patients) and girls (33%). Eighty percent of the cases occurred in children aged 6–24 months. In 18 children AHEI developed less than 15 days after immunization, including combined vaccination. In both reviews the authors noted that some cases were preceded by active immunization. Ting considered vaccinations including HA, HB, influenza, and H1N1 as potential triggers of CV in children [10].

We could not identify a uniformly used definition of SOCV in the published vaccine safety literature. This is a missed opportunity, as data comparability across trials or surveillance systems would facilitate data interpretation and promote the scientific understanding of the event.

1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for single organ cutaneous vasculitis as an adverse events following immunization

Following the process described in the overview paper [35] as well as on the Brighton Collaboration Website https://brighton-collaboration.org/public/what-we-do/setting-standards/case-definitons.html, the Brighton Collaboration Single Organ Cutaneous Vasculitis Working Group was formed in 2014 and included members of academic and public health background.

To guide the decision-making for the case definition and guidelines, a literature search was performed using PubMed (Medline) and EMBASE including the terms vasculitis, immunization and all terms included in the Chapel Hill Consensus Conference 2012 [4]. We applied the same search strategy published in the general vasculitis paper by Bonetto et al. [36]. Articles related to Single Organ Cutaneous Vasculitis were extracted. Using this systematic search we found fifteen articles about CV following immunization (13 case reports, 1 case series and 2 reviews).

1.3. Rationale for selected decisions about the case definition

1.3.1. The term single organ cutaneous vasculitis (SOCV)

Several terms were used in the past and some of them are still applied in clinical practice to diagnose CV (see paragraph 1.1). Synonyms for small vessel vasculitis of the skin [6] include “leukocytoclastic vasculitis”, “hypersensitivity vasculitis”, “cutaneous leukocytoclastic angiitis” “cutaneous small vessel vasculitis”. The term “single organ vasculitis” is included in the CHCC 2012 nomenclature, and in order to be in line with this classification, and to be more specific, we have added the word “cutaneous” [4]. Therefore, the proposed case definition of SOCV aims to capture cutaneous manifestations of vasculitis presenting with typical lesions for either of the phenotypes (leukocytoclastic vasculitis, CSVV, UV, AHEI) possibly accompanied by mild symptoms (low grade fever, mild arthralgia, malaise). Features of systemic vasculitis disease must have been excluded by clinical history, physical examination and selected laboratory exams.

1.3.2. Formulating a case definition that reflects diagnostic certainty: weighing specificity versus sensitivity

It needs to be re-emphasized that the definition levels are entirely about diagnostic certainty, not clinical severity of the event. Thus, a clinically very severe event may appropriately be classified as Level 2 or Level 3 rather than Level 1, if it could reasonably be of non-cutaneous vasculitis etiology. Detailed information about the severity of the event should additionally always be recorded, as specified by the data collection guidelines.

The number of symptoms and/or signs that will be documented for each case may vary considerably. The case definition has been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, two additional diagnostic levels have been included in the definition, offering a stepwise increase of sensitivity from Level 1 down to Level 3, while retaining an acceptable level of specificity at all levels. In this way it is hoped that all possible cases of SOCV can be captured.

The most frequent scenarios in CV reports have been taken into account in the creation of the different levels of diagnostic certainty.

Level 1 of diagnostic certainty (certain) is satisfied when clinical and histological criteria are present and consistent with SOCV. Level 2 of diagnostic certainty (probable) is satisfied when clinical features are consistent with vasculitis and skin biopsy have been performed but the results are not fully conclusive (fibrinoid necrosis is lacking). This could also be due to the timing and the type of the lesion biopsied. Level 3 (possible) is met when clinical features are consistent with cutaneous vasculitis but skin biopsy has not been performed. A simplified diagnostic algorithm is shown in Fig. 1. Additional categories, for events that do not meet the case definition, are Level 4 (reported SOCV with insufficient evidence to meet the case definition) and Level 5 (not a case of SOCV).

1.3.3. Pathology findings

Since skin biopsy is the gold standard for diagnosis, histological features consistent with vasculitis are included in the level 1 and 2 of this case definition. A punch biopsy is generally sufficient and should ideally be performed when the cutaneous lesion is relatively “fresh” yet well-established, that is, roughly 24–48 h old.

The natural progression of CSVV ranges from IC deposition to inflammatory infiltration, vessel disruption, thrombosis, necrosis, and healing [6]. The histological features in UV are similar to that of typical CSVV. AHEI lesions show a perivascular neutrophilic infiltration with leukocytoclastia (fragmentation of nuclei) of small vessels. Direct immunofluorescence shows a predominance of IgM (80%), IgA (30%) IgE (30%) or IgG (20%), in contrast with that of HSP, in which IgA predominates. Furthermore, there has been evidence of C1q deposition in AHEI but not in HSP [10]. It is important to note that these histologic patterns are typical but not specific for any particular type of vasculitis. Infections, insect bite reactions, neutrophilic dermatoses, and ulcers due to other causes may all exhibit leukocytoclastic vasculitis secondary to the primary process. Clinical-pathologic correlation, as always, is necessary before etting on a final diagnosis [6].

1.3.4. Laboratory findings

Exclusion of systemic manifestations is mainly based on clinical history and physical examination. However, a selected and targeted laboratory workup has been included in this case definition to increase the diagnostic certainty for SOCV (Levels 1, 2, 3).

1.3.5. Influence of treatment on fulfilment of case definition

The Working Group decided against using “treatment” or “treatment response” towards fulfilment of the SOCV case definition. A treatment response or its failure is not by itself diagnostic, and may depend on variables like clinical status, time to treatment, and other clinical parameters. For example, even though corticosteroids are still the mainstay of vasculitis treatment, this treatment is not specific to SOCV and is frequently used to treat other systemic autoimmune conditions and others that could mimic SLE (e.g. allergic reaction). Hence, we designed the Level Two and Level Three definitions to be broad enough to include cases presenting differently due to appropriate and early treatment initiation.
1.3.6. Timing post immunization

Specific time frames for onset of symptoms following immunization are not included for the following main reasons: the etiological spectrum of SOCV remains to be elucidated. It is unclear whether SOCV may be induced or promoted by specific single or cumulative exposures. Defining a time to onset of disease is not possible based on the current pathophysiologic understanding of the disease. The potential role of immunization in this process also remains to be elucidated. At this point of scientific learning it would be premature to include a time post immunization in the case definition. Further, we postulate that a case definition designed to be a suitable tool for testing causal relationships requires ascertainment of the outcome (e.g. SOCV) independent from the exposure (e.g. immunizations). Therefore, to avoid selection bias, a restrictive time interval from immunization to onset of SOCV should not be an integral part of such a definition. Instead, we suggest harmonized increments of data analysis to promote data comparability as described in the data analysis guidelines below.

1.3.7. Differential diagnosis

The differential diagnosis of SOCV with small vessel involvement should include vasculitides with systemic or other organ involvement. Other disorders that involve small blood vessels and could mimic a CV are infections, hemorrhage, thrombosis (livedoid vasculopathy), and vascular wall pathology (amyloidosis) [5]. Several disorders can also present with skin lesions that resemble cutaneous manifestations of vasculitis: palpable purpura in case of arthropod bites, morbilliform drug eruptions with hemorrhage in dependent sites, erythema multiforme, pityriasis lichenoides et varioliformis acuta, infectious emboli, lichenoid capillaritis (chronic pigmented purpura), cellulitis; for other lesions such as urticarial lesions, ulcers, nodules the clinical differential diagnosis includes a series of reactive, infective, inflammatory, autoimmune, neoplastic and paraneoplastic diseases [1].

1.4. Guidelines for data collection, analysis and presentation

The case definition is accompanied by guidelines on data collection, analysis and presentation, which may be used for conducting clinical research or reporting cases. The case definition and guidelines are not intended to guide or establish criteria for management of patients. Both were developed to improve data comparability.

1.5. Periodic review

Similar to all Brighton Collaboration case definitions and guidelines, review of the definition with its guidelines is planned on a regular basis (i.e. every three to five years) or more often if needed.
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<th>Title</th>
<th>Vaccine type</th>
<th>Association yes/no/possible according to author</th>
<th>Age range or mean</th>
<th>No of reported cases</th>
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<td>Influenza vaccination</td>
<td>Not specified</td>
<td>17-year-old girl</td>
<td>1</td>
<td>Taiwan</td>
<td>Yes</td>
</tr>
<tr>
<td>Sedaghat et al.</td>
<td>2007</td>
<td>Cutaneous vasculitis</td>
<td>Case report</td>
<td>Panuveitis and dermal vasculitis following MMR vaccination</td>
<td>MMR</td>
<td>Possible</td>
<td>17-year-old girl</td>
<td>1</td>
<td>Iran</td>
<td>Yes</td>
</tr>
<tr>
<td>Tavadia et al.</td>
<td>2003</td>
<td>Leukocytoclastic</td>
<td>Case series</td>
<td>Leukocytoclastic vasculitis and influenza vaccination</td>
<td>Influenza vaccination</td>
<td>Possible</td>
<td>Mean age 75 yr old</td>
<td>4</td>
<td>UK</td>
<td>Yes</td>
</tr>
<tr>
<td>Ulm et al.</td>
<td>2006</td>
<td>Leukocytoclastic</td>
<td>Case report</td>
<td>Leukocytoclastic vasculitis and acute renal failure after influenza vaccination in an elderly patient with myelodysplastic syndrome</td>
<td>Influenza vaccination</td>
<td>Yes</td>
<td>70-year-old male</td>
<td>1</td>
<td>Germany</td>
<td>Yes</td>
</tr>
<tr>
<td>Walker et al.</td>
<td>2004</td>
<td>Leukocytoclastic</td>
<td>Case report</td>
<td>Leukocytoclastic vasculitis and influenza immunization</td>
<td>Influenza vaccination</td>
<td>Possible</td>
<td>64-year-old woman</td>
<td>1</td>
<td>UK</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BCG: Bacille Calmette-Guerin; HAV: Hepatitis A vaccination; HBV: Hepatitis B vaccination; HPV: Human Papillomavirus; MMR: Measles, Mumps, and Rubella vaccination.
2. Case definition of single organ cutaneous vasculitis

SOCV is a syndrome characterized by clinical and histological features of small vessel vasculitis of the skin without involvement of other organ systems.

2.1. For all levels of diagnostic certainty

Clinical features

- Hemorrhagic papules
- Urticaria-like lesions
- Purpuric rash involving the face, ears, and extremities

Histology

- Perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei (leukocytoclasia)
- Erythrocyte extravasation or haemorrhage into the dermis
- Fibrinoid necrosis or degeneration of the dermal postcapillary venules
- Lymphocytic small vessel vasculitis

Exclusion of other organ or systemic involvement

- Normochromic normocytic anemia, thrombocytopenia
- Renal involvement (proteinuria, haematuria, hypertension, increased serum creatinine)
- Pulmonary involvement (dyspnea, cough, hemoptysis, patchy or diffuse alveolar infiltrates in chest X-ray)
- Gastrointestinal involvement (abdominal pain, vomiting, gas-
trointestinal bleeding)
- Liver involvement (elevated liver enzymes and bilirubin)
- Serosal involvement (pericardial and or pleural effusion) with ultrasound and/or X-ray examination in case of clinical suspicion
- Arthritis (synovitis) with synovial aspirate in case of clinical suspicion
- Central or peripheral nervous system involvement by neurologic physical examination
- Presence of antinuclear antibodies, ANCA, rheumatoid factor, anti-citrullinated peptides antibodies (CCP), cryoglobulins
- Reduced serum complement factors (C3, C4, C1q)

2.2. Level 1 of diagnostic certainty

Histology

Perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei (leukocytoclasia) AND Erythrocyte extravasation or haemorrhage into the dermis AND Fibrinoid necrosis or degeneration of the dermal postcapillary venules

Exclusion of other vasculitic organ system involvement


2.3. Level 2 of diagnostic certainty

Histology:

Perivascular inflammatory cells infiltrates dominated by neutrophils with fragmented nuclei (leukocytoclasia) AND Erythrocyte extravasation or haemorrhage into the dermis AND Exclusion of other organ or systemic involvement (see Level 1).

2.4. Level 3 of diagnostic certainty

Histology - not available

Exclusion of other organ or systemic involvement (see Level 1).

3. Guidelines for data collection, analysis and presentation on single organ cutaneous vasculitis

It was the consensus of the Brighton Collaboration SOCV Working Group to recommend the following guidelines to enable meaningful and standardized collection, analysis, and presentation of information about cutaneous vasculitis without systemic involvement. However, implementation of all guidelines might not be possible in all settings. The availability of information may vary depending upon resources, geographical region, and whether the source of information is a prospective trial, a post-marketing surveillance or epidemiological study, or an individual report of SOCV. These guidelines have been developed by this working group for guidance only, and are not to be considered a mandatory requirement for data collection, analysis, and presentation.

3.1. Data collection

These guidelines represent a desirable standard for the collection of data to allow for comparability of data between studies and are recommended as an addition to data collected for a specific study question and setting. The guidelines are not intended to constrain primary reporting of SOCV in surveillance systems or study monitoring. Investigators developing a data collection tool based on these data collection guidelines also need to refer to the criteria in the case definition, which are not repeated in these guidelines.

The following guidelines represent a desirable standard for collection of vaccine safety data. In accordance with general drug safety guidelines by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as the form for reporting of drug adverse events developed by the Council for International Organizations of Medical Sciences (CIOMS), data elements to be collected for the assessment of an AEI are an identifiable reporter and patient, one or more prior immunizations, and a detailed description of the adverse event; in this case, of SOCV following immunization [37,38]. Additional guidelines have been developed as guidance for the collection of additional information to allow for a more comprehensive understanding of SOCV following immunization.

3.1.1. Source of information/reporter

For all cases and/or all study participants, as appropriate, the following information should be recorded:

- Other lesions (necrosis, ulcers, petechiae, hemorrhagic bullae, pustules) may also be present.
- Erythematous-edematous lasting longer than 24 h leaving bruising or hyperpigmentation when disappearing; Pain or burning rather than itching sensation may be present.
- Fibrinoid and/or thrombotic obliteration of affected vessels may be present.
- Lymphocytes and eosinophils may be present or even predominate (e.g., lymphocytic small vessel vasculitis).
- Other small vessel walls may also be affected.
- Fibrinoid and/or thrombotic obliteration of affected vessels may be present.
- Direct immunofluorescence, if available, may show a predominance of immunoglobulins IgM and IgG, and C3.
- The list is only exclusionary if these features are likely due to vasculitis in other organs. Joint pain, abdominal pain, gastrointestinal tract bleeding, intussusception, scrotal pain, testicular torsion and periorbital edema have been described in AHEI, even though very rarely.
For all cases and/or all study participants, as appropriate, the following information should be recorded:

- Date of report.
- Name and contact information of person reporting and/or diagnosing the SOCV as specified by country-specific data protection law.
- Name and contact information of the investigator responsible for the subject, as applicable.
- Relation to the patient (e.g., immuniser [clinician, nurse], family member [indicate relationship], other).

3.1.2. Vaccinee/control

3.1.2.1. Demographics. For all cases and/or all study participants, as appropriate, the following information should be recorded:

- Case/study participant identifiers (e.g. first name initial followed by last name initial) or code (or in accordance with country-specific data protection laws).
- Date of birth, age, and sex.
- For infants: Gestational age and birth weight.

3.1.3. Clinical and immunization history

For all cases and/or all study participants, as appropriate, the following information should be recorded:

- Past medical history, including hospitalisations, underlying diseases/disorders (including febrile diseases), pre-immunization signs and symptoms including identification of indicators for, or the absence of, a history of allergy to vaccines, vaccine components or any medications; food allergy; allergic rhinitis; atopic eczema; asthma, autoimmune diseases.
- Any medication history (other than treatment for the event described) prior to, during, and after immunization including prescription and non-prescription medications as well as medications or treatments with long half-life or long term effect (e.g. immunoglobulins, blood transfusion and immunosuppressants).
- Immunization history (i.e. previous immunizations and any adverse event following immunization (AEFI), in particular occurrence of SOCV after a previous immunization.

3.1.4. Details of the immunization

For all cases and/or all study participants, as appropriate, the following information should be recorded:

- Date and time of immunization(s).
- Description of vaccine(s) (name of vaccine, manufacturer, lot number, dose [e.g. 0.25 mL, 0.5 mL, etc] and number of dose if part of a series of immunizations against the same disease). Details regarding vaccine diluent, if present in a separated vial.
- The anatomical sites (including left or right side) of all immunizations (e.g. vaccine A in proximal left lateral thigh, vaccine B in left deltoid).
- Route and method of administration (e.g. intramuscular, intradermal, subcutaneous, and needle-free [including type and size], other injection devices).
- Needle length and gauge.

3.1.5. The adverse event

For all cases at any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet the case definition should be recorded.

Specifically document:

- Clinical description of signs and symptoms of SOCV, and if there was medical confirmation of the event (i.e. patient seen by a physician, general practitioner or specialist).
- Date/time of onset, first observation and diagnosis, end of episode and final outcome.
- Concurrent signs, symptoms, and diseases.
- Measurement/testing
  - Values and units of routinely measured parameters (e.g. temperature, blood pressure) – in particular those indicating the severity of the event;
  - Method of measurement (e.g. type of thermometer, oral or other route, duration of measurement, etc.);
  - Results and time of laboratory examinations and pathological findings on biopsy;
  - Results of radiological/ultrasonography examinations,
- Treatment given for SOCV (topical or systemic).
- Outcome (see footnote 6#) at last observation. Residual lesions, including scars and hyper- or hypo pigmentation.
- Objective clinical evidence supporting classification of the event as “serious”.
- Exposures other than the immunization within 6 weeks before and after immunization (e.g. food, environmental) considered potentially relevant to the reported event.

3.1.6. Miscellaneous/general

The duration of surveillance for SOCV should be predefined based on

- Biologic characteristics of the vaccine e.g. live attenuated versus inactivated component vaccines;
- Biologic characteristics of the vaccine-targeted disease;
- Biologic characteristics of SOCV including patterns identified in previous trials (e.g. early-phase trials); and
- Biologic characteristics of the vaccinee (e.g. nutrition, underlying disease like immunodepressing illness).

The duration of follow-up reported during the surveillance period should be predefined likewise. It should aim to continue to resolution of the event.

Methods of data collection should be consistent within and between study groups, if applicable.

Follow-up of cases should attempt to verify and complete the information collected as outlined in data collection guidelines 1–24.

Investigators of patients with SOCV should provide guidance to reporters to optimise the quality and completeness of information provided.

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10 If the reporting centre is different from the vaccinating centre, appropriate and timely communication of the adverse event should occur.

11 The date and/or time of onset is defined as the time post immunization, when the first sign or symptom indicative for SOCV occurred. This may only be possible to determine in retrospect.

12 The date and/or time of first observation of the first sign or symptom indicative for SOCV can be used if date/time of onset is not known.

13 The date of diagnosis of an episode is the day post immunization when the event met the case definition at any level.

14 The end of an episode is defined as the time the event no longer meets the case definition at the lowest level of the definition.

15 For example, recovery to pre-immunization health status, spontaneous resolution, therapeutic intervention, persistence of the event, sequelae, death.

16 An AEFI is defined as serious by international standards if it meets one or more of the following criteria: (1) it results in death, (2) is life-threatening, (3) it requires inpatient hospitalisation or results in prolongation of existing hospitalisation, (4) results in persistent or significant disability/incapacity, (5) is a congenital anomaly/birth defect, (6) is a medically important event or reaction.
(30) Reports of SOCV should be collected throughout the study period regardless of the time elapsed between immunization and the adverse event. If this is not feasible due to the study design, the study periods during which safety data are being collected should be clearly defined.

3.2. Data analysis

The following guidelines represent a desirable standard for analysis of data on SOCV to allow for data comparability, and are recommended as an addition to data analysed for the specific study question and setting.

(31) Reported events should be classified in one of the following five categories including the three levels of diagnostic certainty. Events that meet the case definition should be classified according to the levels of diagnostic certainty as specified in the case definition. Events that do not meet the case definition should be classified in the additional categories for analysis.

3.2.1. Event classification in 5 categories

3.2.1.1. Event meets case definition.

- Level 1: Criteria as specified in the SOCV case definition.
- Level 2: Criteria as specified in the SOCV case definition.
- Level 3: Criteria as specified in the SOCV case definition.

3.2.1.2. Event does not meet case definition.

3.2.1.2.1. Additional categories for analysis.

- (4) Reported SOCV with insufficient evidence to meet the case definition (Level 4).
- (5) Not a case of SOCV (Level 5).
- (32) The interval between immunization and reported SOCV could be defined as the date/time of immunization to the date/time of onset (see Footnote 11) of the first symptoms and/or signs consistent with the definition. If few cases are reported, the concrete time course could be analysed for each; for a large number of cases, data can be analysed in the following increments:

<table>
<thead>
<tr>
<th>Interval after immunization</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 h</td>
<td></td>
</tr>
<tr>
<td>2–3 days</td>
<td></td>
</tr>
<tr>
<td>4–7 days</td>
<td></td>
</tr>
<tr>
<td>8–14 days</td>
<td></td>
</tr>
<tr>
<td>14–21 days</td>
<td></td>
</tr>
<tr>
<td>&gt;21 days (with 7 day increments thereafter up to 2 months)</td>
<td></td>
</tr>
<tr>
<td>3–12 months (with 1 month increments)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

3.2.1.2.2. Subjects with SOCV by interval to presentation

(33) The duration of a possible SOCV could be analysed as the interval between the date/time of onset (see Footnote 1#) of the first symptoms and/or signs consistent with the definition and the end of episode (see Footnote 5#) and/or final outcome (see Footnote 15). Whatever start and ending are used, they should be used consistently within and across study groups.

(34) If more than one measurement of a particular criterion is taken and recorded, the value corresponding to the greatest magnitude of the adverse experience could be used as the basis for analysis. Analysis may also include other characteristics like qualitative patterns of criteria defining the event.

(35) The distribution of data (as numerator and denominator data) could be analysed in predefined increments (e.g. measured values, times), where applicable. Increments specified above should be used. When only a small number of cases is presented, the respective values or time course can be presented individually.

(36) Data on SOCV obtained from subjects receiving a vaccine should be compared with those obtained from an appropriately selected and documented control group(s) to assess background rates of hypersensitivity in non-exposed populations, and should be analysed by study arm and dose where possible, e.g. in prospective clinical trials.

3.3. Data presentation

These guidelines represent a desirable standard for the presentation and publication of data on SOCV following immunization to allow for comparability of data, and are recommended as an addition to data presented for the specific study question and setting. Additionally, it is recommended to refer to existing general guidelines for the presentation and publication of randomised controlled trials, systematic reviews, and meta-analyses of observational studies in epidemiology (e.g. statements of Consolidated Standards of Reporting Trials (CONSORT) [39], of Improving the quality of reports of meta-analyses of randomised controlled trials (QUORUM) [40], and of meta-analysis of Observational Studies in Epidemiology (MOOSE) [41], respectively).

(37) All reported events of SOCV should be presented according to the categories listed in guideline 31.

(38) Data on possible SOCV events should be presented in accordance with data collection guidelines 1–24 and data analysis guidelines 31–36.

(39) Terms to describe SOCV such as “low-grade”, “mild”, “moderate”, “high”, “severe” or “significant” are highly subjective and prone to misinterpretation, and should be avoided, unless clearly defined.

(40) Data should be presented with numerator and denominator (n/N) (and not only in percentages), if available. Although immunization safety surveillance systems denominator data are usually not readily available, attempts should be made to identify approximate denominators. The source of the denominator data should be reported and calculations of estimates be described (e.g. manufacturer data like total doses distributed, reporting through Ministry of Health, coverage/population based data, etc.).

(41) The incidence of cases in the study population should be presented and clearly identified as such in the text.

(42) If the distribution of cases is skewed, median and range are usually the more appropriate statistical descriptors than a mean. However, the mean and standard deviation should also be provided.

(43) Any publication of data on SOCV should include a detailed description of the methods used for data collection and analysis as possible. It is essential to specify:

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17 The highest possible level of classification should be recorded for each event.
18 If the evidence available for an event is insufficient because information is missing, such an event should be categorised as “Reported SOCV with insufficient evidence to meet the case definition”.
19 An event does not meet the case definition if investigation reveals a negative finding of a necessary criterion (necessary condition) for diagnosis. Such an event should be rejected and classified as “Not a case of SOCV”.

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Conflict of interest

Giovanna Zanoni, Roberta Opri, Caterina Bonetto, Francesco Trotta, Peter Hausermann, Jan Bonhoeffer have no conflict of interest to disclose. Giampietro Girolomoni has been principal investigator in clinical trials and has received personal fee from many pharmaceutical companies. Nothing directly relevant to this article.

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Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant’s organisation (e.g., government, university, or corporation). Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Italian Medicines Agency.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.09.032.

References


Use of this document should preferably be referenced by referring to the respective link on the Brighton Collaboration website (http://www.brightoncollaboration.org).