Indications and limitations of histopathological skin investigation of Henoch–Schönlein purpura in children

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Abstract

Henoch–Schönlein purpura, the most common primary vasculitis of the child, may cause, in some cases with atypical clinical picture, diagnostic difficulties with a significant prognosis impact, especially when occasionally “silent” renal symptoms coexist. The purpose of our study is, on one hand, to determine the histopathological investigation needs of Henoch–Schönlein purpura in children with atypical cutaneous manifestations or incomplete forms of illness and, on the other hand, to point out the correlation between the cutaneous histopathological aspects and other clinical and biological manifestations.

Results: Optical microscopy revealed signs of leukocytoclastic vasculitis in 11 of the 22 cases with ulcerative necrotic purpura and atypical clinical picture. Immunohistochemical examination proved that these were associated with IgA deposits on the vascular wall, sometimes accompanied by C3, fibrin, IgM and CD3. The severity of the skin manifestations was directly correlated with the severity of digestive and/or renal symptoms. Conclusions: Skin biopsy is indicated only in the atypical or incomplete forms of disease to support positive diagnosis by immunohistochemical evidence of the vascular IgA deposits. The severity and persistence of the ulceronecrotic purpuric rash seems to be directly related rather to the severity of the other clinical manifestations (digestive or renal) than to the generalized extensively purpuric appearance.

Keywords: Henoch–Schönlein vasculitis, skin, immunohistochemical exam, children.

Introduction

Henoch–Schönlein purpura (HSP), the most common IgA-mediated primary immune vasculitis in children, is characterized by a set of clinical symptoms of variable severity, namely purpuric lesions, osteoarticular, intestinal and sometimes renal manifestations, which determine the disease prognosis [1, 2]. Although the clinical and biological manifestations are specific and classifiable according to the 1990 ACR or 2007 EULAR disease diagnosis criteria in over 80% of the cases, the isolated or atypical manifestations may cause diagnostic difficulties in the remaining patients and hence require more thorough explorations [3, 4]. Thus, these particular cases are prone to the occurrence of “silent” life-threatening kidney damage, which may ultimately lead to chronic renal failure in the absence of therapy. An over diagnosis risk is also likely in these cases, which involves additional patient monitoring and care costs.

The purpose of this study is, on one hand, to determine the histopathological investigation needs of Henoch–Schönlein purpura in children with atypical cutaneous manifestations or incomplete forms of illness and, on the other hand, to point out the correlation between the cutaneous histopathological aspects and other clinical and biological manifestations.

Patients and Methods

The retrospective study was conducted on a group of 183 children (1–18-year-old) diagnosed with HSP, in the IIth Clinic of Pediatrics from “St. Mary” Pediatric Emergency Hospital from Iassy in the period 1995–2006. The criteria for inclusion in the study were: patient and family consent, HSP diagnostic according to ACR criteria (1990)/EULAR (2006), minimum three controls in the first year after onset of disease. Of this group, 22 children were chosen (12.68%) showing less characteristic skin lesions and no other features suggestive of disease within the ACR diagnostic criteria.

In order to complete the diagnostic criteria, skin biopsy was performed in 11 of the 22 cases exhibiting atypical clinical and cutaneous symptomatology. The skin biopsy cups were examined in light microscopy (Hematoxylin–Eosin and Giemsa stain) and immunohistochemistry. The immunohistochemical examination was performed on paraffin samples coming from skin biopsies and used monoclonal anti-IgA, IgM, CD3 (for
T-lymphocyte) antibodies. The samples were examined using a Nikon microscope, and the specific immunomarking was revealed by the brown precipitate that occurred on the samples.

Results

Of the 183 cases of HSP, the necrotic ulcerative skin purpura was found in 12.68% (22 cases) mainly in the 6–12-year-old group (16/22 cases), followed by the 12–16-year-old group (5/22 cases) (Figure 1).

None of the patients included in the research group exhibited persistent or recurrent ulceroc-necrotic purpura (>21 days). The average evolution period was 14–21 days in these studies, as compared to 5.32 days in the classical form. In 11/22 cases, for diagnostic purposes, the histopathological investigation was required because of the atypical clinical aspect of the disease (Table 1).

Table 1 – Atypical clinical forms of HSP

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38.5°C</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>ASAT, ALAT ×1.5 NV</td>
<td>4</td>
</tr>
<tr>
<td>Cough and dyspnea</td>
<td>4</td>
</tr>
<tr>
<td>Inflammatory syndrome</td>
<td>11</td>
</tr>
</tbody>
</table>

The histopathological appearance in optical microscopy was the leukocytoclastic vasculitis with vascular and perivascular polymorphonuclear infiltration in 9/11 cases and necrotizing vasculitis aspects in 2/11 cases (Figures 2 and 3).

The immunohistochemical examination supported the diagnostic exploration and revealed IgA, IgM and CD3 deposits on the vascular wall (Figures 4–6).

The analysis of the patients with ulceroc-necrotic purpuric cutaneous lesions proved a more frequent and severe occurrence of gastrointestinal and/or renal symptoms in these patients than in those suffering from the classical form of the disease with non-ulcerated purpuric lesions. Thus, upper gastrointestinal bleeding occurred in 14.3% cases vs. 5.1% in the classical distribution of purpuric lesions, abdominal pain in 82.3% vs. 65.6% in the classical cases, and dyspeptic syndrome in 64.3% vs. 16.3% in the classical form (Figure 7).

The renal symptomatology, even more severe when ulceroc-necrotic skin lesions were involved, was obvious: oliguria in 17.6% vs. 14.1% in the classical form of purpura, hypertension (HTA) in 11.7% vs. 1.9%, macroscopic hematuria in 45.4% vs. 5.19%, and microscopic hematuria in 76.4% vs. 39.2% (Figure 8).

However, the average number of relapses in these patients or the incidence of renal problems caused by these relapses was not different from the average number of relapses in patients with the classical form of the disease (palpable purpura on the legs and buttocks or generalized purpura). Although this particular type of purpuric injury is more frequently associated with severe digestive and renal conditions, the streptococcal infection incidence in the medical history of these patients is less obvious than in other cases. The streptococcal infection was supported by the high serologic level of ASLO in 23.5% of the cases (5/22 cases), as compared with 36.6% of the patients suffering from the classical form of the disease with purpuric skin injury on the legs and buttocks and with 12% of the patients exhibiting generalized purpuric rash (Figure 9).

The presence of Group A microbiological β-hemolitic streptococcus (βHSA) (throat swab) was revealed in 17.6% of the ulceronecrotic patients and in 17.8% of the classical cutaneous lesion patients, respectively, as compared to only 6.1% of the generalized purpura patients (Figure 10).
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Figure 4 – Henoch–Schönlein purpura (IgA immunostaining, ×100).

Figure 5 – Henoch–Schönlein purpura (IgM immunostaining, ×100).

Figure 6 – Henoch–Schönlein purpura (CD3 immunostaining, ×200).

Figure 7 – Correlation between cutaneous purpura aspects and gastrointestinal damage.

Figure 8 – Correlation between cutaneous purpura aspect and renal damage.


**Discussion**

The ACR criteria (1990) for HSP (sensitivity 87.1%, specificity 87.7%) require the presence of at least two of the following: (1) age ≤20 years at disease onset; (2) palpable purpura; (3) acute abdominal pain; (4) biopsy showing granulocytes in the walls of small arterioles/venules [5, 6]. Positive diagnosis criteria have been reviewed and set by the European League Against Rheumatism (EULAR-2006) as follows [7]: purpura or petechiae (mandatory criterion) with lower limb predominance, which meets at least one of the four following criteria: (1) abdominal pain; (2) histopathology (typically leukocytoclastic vasculitis with prevailing IgA deposits or proliferative glomerulonephritis with prevailing IgA deposits); (3) arthritis or arthralgia; (4) renal involvement.

The debut of the disease is usually reported in 20–30% of cases after an upper respiratory tract infection, the most common being the one of streptococcal etiology (βHSA) after vaccination or the consumption of certain drugs [8, 9]. In the observed group, there were no statistically significant differences of infection rate of βHSA in the classical HSP vs. the atypical form. The non-pruritic cutaneous purpuric lesions, which disappear in the first hours of evolution due to viremia, occur in all the patients of the initial study group and have a polymorphic clinical appearance (palpable, hemorrhagic, urticarial, petechiae, ulcerated and necrotic or bullous purpuric lesions), and an evolution consisting of successive relapses when standing. The skin lesions appear especially on the devious areas and their disposition is symmetrical and metamerical, as they occur mostly on the buttocks and legs. It is rarely generalized, yet it always respects the palms and soles [10, 11]. There are also even rarer cases when the skin lesions are ulcerated and necrotic or atypical and when the clinical picture is not suggestive of this disease. Hence, further histopathological investigations are required for diagnostic purposes [12–14]. 12.68% (22 cases) of the patients included in the study group had an unspecific clinical picture and therefore skin biopsy was performed in 11/22 of them. Skin biopsy is neither a current compulsory stage in diagnostic setting, nor a useful marker in disease evolution tracing [15]. Optical microscopy examination is for orientation purposes only, as it detects leukocytoclastic vasculitis, but this is also characteristic of other pathologic entities such as: drug reactions, malignancies, collagen diseases (systemic lupus erythematosus, juvenile idiopathic arthritis), infection (brucellosis), mixed cryoglobulinemia associated with hepatitis C infection and other immune vasculitis (periarteritis nodosa, Behçet disease, Wegener granulomatosis) [16–18]. A certain histopathological diagnosis is set only by immunohistochemistry or immunofluorescence examination, which detects the vascular IgA deposits [19]. The immunohistochemical examination performed in the 11 clinically atypical cases revealed IgM and CD3 deposits in addition to the vascular and perivascular IgA ones. On one hand, this supported the Henoch–Schönlein vasculitis diagnosis, and, on the other hand, it proved the involvement of cellular immunity in the complex pathogenesis of the disease. Takeuchi S et al. indicated a possible connection between IgM in cutaneous lesions in adults with Henoch–Schönlein vasculitis and renal involvement [20]. In particular it was noted that the severity of skin lesions appears directly linked to the severity of the other symptoms of the disease, consequently in these children the incidence of severe gastrointestinal symptoms (abdominal pain, dyspepsia, upper gastrointestinal hemorrhage) was higher than in patients who presented the classical form of skin rash (on the legs and buttocks). The same aspect of the severity of clinical and laboratory expression is highlighted in the report with renal manifestations. Thus, hematuria (particularly macroscopic), hypertension, edema and oliguria were more frequent in these patients than in the other patients. In a study conducted to assess the risk factors of renal involvement, Sano et al. also describe persistent cutaneous purpura (≥1 month) of varying degrees of severity among other criteria. A single patient in our group exhibited persistent ulcerated and necrotic cutaneous purpura (for more than three weeks). The renal biopsy performed on this patient also revealed mesangioproliferative glomerulonephritis [21].

**Conclusions**

Skin biopsy is indicated only in atypical or incomplete forms to support the diagnosis of the disease. The severity and persistence of the purpuric rash (the ulcero-necrotic type) seems to be directly correlated with the severity of other clinical manifestations in the clinical picture (digestive or kidney) more than their extensively (generalized) purpuric appearance. The risk of the renal association increases with the severity and especially the persistence of the skin lesion. The immunohistochemical objectification of the deposits...
of IgA at vascular level is an important diagnostic marker in the atypical forms, on the other hand supporting the involvement of IgA in the pathogenic mechanism of the Henoch–Schönlein purpura.

References

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