Non-thrombocytopenic purpura in familial Mediterranean fever—comorbidity with Henoch–Schönlein purpura or an additional rare manifestation of familial Mediterranean fever?

Eldad Ben-Chetrit and Hasan Yazici

Abstract
Henoch–Schönlein purpura is a relatively common vasculitis mainly affecting children. It is characterized by purpuric skin rash, abdominal cramping, and haematuria. Skin biopsies taken from Henoch–Schönlein purpura lesions disclose perivascular IgA deposits. FMF is an autoinflammatory disease characterized by recurrent attacks of fever lasting 2–3 days which resolve spontaneously. Typical manifestations of the disease are peritonitis, pleuritis, pericarditis, arthritis and erysipelas-like erythema usually affecting the lower limbs. Over the years many reviews emphasized the clinical impression that Henoch–Schönlein purpura is more common among FMF patients than in healthy control population. In this review we summarize these reports and show that sometimes Henoch–Schönlein purpura associated with FMF differs from typical isolated Henoch–Schönlein purpura, and this is also the case with polyarteritis nodosa and SpA associated with FMF. It is suggested that these clinical manifestations (polyarteritis nodosa, Henoch–Schönlein purpura and SpA) should be considered to be associated with FMF as part of what we call FMF rather than as co-existing additional separate clinical entities.

Key words: familial Mediterranean fever, Henoch–Schönlein purpura, polyarteritis nodosa

Rheumatology key messages
● Non-thrombocytopenic purpura is more common in FMF than in the general population.
● Non-thrombocytopenic purpura in FMF patients has no IgA deposits, can be recurrent and may affect the face and trunk.
● Non-thrombocytopenic purpura in FMF patients should be considered an integral clinical feature of FMF.

Introduction
In 1837, Johann Lukas Schönlein described a patient with allergic non-thrombopenic purpuric rash associated with joint pain [1]. In 1868 Eduard Heinrich Henoch, his student, described the association of colic abdominal pain, bloody diarrhoea, painful joints and rash in the condition that is known today as Henoch–Schönlein purpura [2].

Henoch–Schönlein purpura is the most common vasculitis syndrome of childhood. It is also known as anaphylactoid purpura, allergic vasculitis, and rarely, as rheumatoid purpura [3]. It is generally a benign, self-limited disorder that follows an intercurrent illness, usually of the upper-respiratory tract. More than 90% of Henoch–Schönlein purpura cases occur in children younger than 10 years; the classic triad of clinical symptoms and signs of Henoch–Schönlein purpura includes purpuric rash (100%), abdominal cramping (60–65%) and haematuria (~40%). However, the spectrum of the clinical expression of Henoch–Schönlein purpura may vary from only minimal petechial rash and joint disease to severe gastrointestinal, renal, pulmonary and neurological disease. Most children recover spontaneously from the disease, and on long-term follow-up, systemic involvement or serious sequelae are not frequent [4]. However, adults with this condition are more likely to experience complications than children [5].
Histopathological features of the skin lesions in infantile Henoch–Schönlein purpura can range from a typical leukocytoclastic vasculitis with or without fibrinoid necrosis to the less specific findings of a lymphohistiocytic perivascular infiltrate with extravasation of erythrocytes.

Direct immunofluorescence testing is a useful adjunct to histopathology; the yield of a positive test result is substantially higher when the test is performed within 48 h of presentation. Immunofluorescence studies reveal perivascular IgA deposition in almost all patients; this finding is rare in Henoch–Schönlein purpura in infants, in which C3 and IgM are most commonly found in the affected vessel walls [6].

Renal histology in Henoch–Schönlein purpura varies considerably [7]. In some cases, most glomeruli appear by light microscopy to be unaffected; only a few show mesangial proliferation. In instances of moderate renal involvement, focal and segmental intracapillary and extracapillary proliferation may be present with adhesions and small crescents. Severe cases are characterized by a diffuse proliferation with infiltration of neutrophils and circumferential crescents in most of the glomeruli. Tubular atrophy and interstitial infiltration with mononuclear cells may also be present. In most patients, IgA deposits in the mesangium and the walls of cutaneous capillaries are detected. The IgA deposited in the mesangium is mainly of the IgA1 subclass, though IgA2 deposits are noted in rare cases. In addition to IgA, the deposits in mesangium and cutaneous capillaries frequently contain C3, IgG and fibrin. C3 deposits are often accompanied by properdin, whereas C1q and C4 are usually not present. These observations suggest that the complement components have been activated by means of the alternative pathway. Additional relatively common feature of Henoch–Schönlein purpura is the elevated serum levels of circulating IgA and/or IgM immune complexes [8].

In 1969 Berger described the presence of mesangial IgA deposition in patients with nephritis [9]. It was proposed that Berger’s kidney disease presents a limited form of Henoch–Schönlein purpura where only the kidneys are involved.

FMF is an autoimmune inflammatory disease characterized by recurrent attacks of fever lasting 2–3 days, resolving spontaneously [10]. Typical manifestations of the disease are peritonitis, pleuritis, pericarditis, arthritis and erysipelas-like erythema usually affecting the lower limbs. Nonspecific purpura may also affect FMF patients. In a study by Majeed et al. [11] this was the most frequent cutaneous manifestation of FMF. Twelve out of 46 FMF patients (26%) had 31 episodes of pink petechiae or blue/black spots with a diameter of 1–2 cm that were macular or just palpable and did not disappear on pressure. They appeared on the face, trunk and extremities including the feet without a special predilection for special sites. Unlike the Henoch–Schönlein rash, they were scattered and not confluent. This rash usually disappeared within 1–3 weeks and was not associated with fever or pruritus. Some patients developed the rash before the onset of FMF and some developed it after the onset. This is probably an integral clinical feature of what we call FMF.

Literature review

Several recent reviews emphasized the clinical impression that vasculitis is more common among FMF patients than in healthy control population [12–15]. Specifically, Henoch–Schönlein purpura and polyarteritis nodosa (PAN) head the list.

The first cases of coincidence of FMF and Henoch–Schönlein purpura were published in 1962, by Rotem and Federgruen [16] (Table 1). These authors described seven patients with Henoch–Schönlein purpura who had FMF and stressed the fact that the course of the disease was severe and stormy, contrasting markedly with the relatively benign course of Henoch–Schönlein purpura in healthy children. However, they did not propose a high frequency of Henoch–Schönlein purpura among the FMF patients. Nor did they provide any detail about the histology of the skin purpuric rash in their patients.

In 1967 Sohar et al. [17] described 470 patients with FMF of whom 17 had Henoch–Schönlein purpura (2.6%). In some of the FMF patients Henoch–Schönlein purpura occurred on several occasions. The authors claimed that the relation between Henoch–Schönlein purpura and FMF was then uncertain.

In 1982 Flatau et al. [18] proposed that FMF and Schönlein-Henoch purpura have a remarkable clinical similarity with episodes of abdominal pains, arthritis, fever, skin eruptions and transient or permanent renal damage in both conditions. Until this publication little attention had been paid to the simultaneous occurrence of both diseases and only 20 cases had been described [16, 17, 19]. In most no details were available regarding the clinical and histopathological features of their disease. Flatau et al. [18] investigated the possible association between FMF and Henoch–Schönlein purpura in their FMF patients who developed Henoch–Schönlein purpura during the years 1966–75. Hospital charts of all the patients diagnosed as suffering from FMF between these years were reviewed. Fifty cases fulfilling the following criteria were included in the Flatau et al. [18] study: recurrent attacks of fever and abdominal pains lasting 1–3 days, with or without joint pain; an elevated erythrocyte sedimentation rate and/or leucocytosis during the attack; absence of other diseases that could explain the clinical picture; and at least a 2-year duration of the disease. The diagnosis of Henoch–Schönlein purpura was based on the following criteria: the appearance of nonthrombocytope- nic purpura with one or several of gastrointestinal tract bleeding, abdominal colicky pains, haematuria, localized oedema and arthritis; and positive results of biopsies from affected skin or kidneys. The authors identified eight FMF patients with Henoch–Schönlein purpura. In four biopsies taken from the skin and two from the kidneys, only in one kidney biopsy was it explicitly said that IgA deposits were not seen. As for the other remaining specimens it is not clear whether IgA deposits were sought for.
In this study also, the authors found that Henoch–Schoenlein purpura had a more severe course compared with those who did not have FMF. Most of them had very high fever (≥39°C) and extreme joint and abdominal pains, and the course of the disease was protracted (2–9 weeks). In most patients, the purpuric rash appeared following penicillin treatment and elevated anti-streptolysin O antibodies suggesting a contributive factor to either penicillin antibiotic or streptococcal infection. Penicillin had previously been mentioned among the probable aetiologic factors of Henoch–Schoenlein purpura [20]. Additional medications such as cefuroxime, vancomycin and NSAIDS have also been implicated in the aetiology of Henoch–Schoenlein purpura [21, 22].

Flatou et al. [18], in the era prior to the identification of the genetic basis of FMF (MEFV gene which encodes pyrin and is associated with FMF, which was isolated in 1997), had suggested that an immunological mechanism played a major role in the pathogenesis of this disease. This suggestion has gained support from the following observations and findings: serum complement consumption was documented during FMF attacks [23, 24], circulating immune complexes were found in 50% of the patients with FMF [25], cold-reacting lymphocytotoxins were detected in the sera of 29% of 69 FMF patients [26], and plasma concentrations of cyclic nucleotides were high during FMF attacks [27]. On the other hand, an immunological pathogenesis for Henoch–Schoenlein purpura had already been suggested at the beginning of the last century, and today it is generally agreed that Henoch–Schoenlein purpura is an immune complex disease [28]. Based upon the above data Flatou et al. [18] concluded that since immune complexes were involved in the pathogenesis of both FMF and Henoch–Schoenlein purpura their coexistence was not coincidental.

In 1983 Schlesinger et al. [29] described a 29-year-old patient suffering from FMF who developed skin rash, severe myalgia and haematuria. Skin biopsy showed vasculitis. The kidney biopsy revealed diffuse proliferative and exudative glomerulonephritis. On immunofluorescence examination, IgM deposits accompanied by C3 were found with a coarse granular peripheral distribution. Electron microscopy revealed glomerular subepithelial deposits. No IgA deposits were demonstrated.

In 1990 Majeed et al. [11] described six FMF patients (13% of the 46 patients studied) who had nine episodes of Henoch–Schoenlein purpura; three patients developed two episodes each. The rash involved mainly the extensor surfaces of the upper and lower extremities. However, unlike the classical distribution of Henoch–Schoenlein purpura, the face and trunk were frequently involved, but the buttocks were involved in only two episodes. With the exception of two severe episodes associated with fever, the general condition of the patients was good and the course of the disease was mild and short (2–3 weeks); remissions occurred spontaneously, without the use of corticosteroids. One patient developed two episodes before the onset of FMF; five episodes occurred in four patients at the onset of FMF, and one patient suffered two episodes after the onset of FMF. A skin biopsy of the rash taken from a single patient showed leucocytoclastic vasculitis and immunofluorescence studies showed deposits of IgG and C3 in the walls of the vessels in the upper dermis. IgA was not sought for.

In 1997 Ozdogan et al. [30] evaluated the frequency of vasculitis, mainly in the forms of Henoch–Schoenlein purpura and PAN among their FMF patients. They reviewed the charts of 207 patients with FMF seen between 1983 and 1993 with respect to clinical vasculitis. In addition they conducted a prospective study, designed to test the presence of occult blood in the first stool specimens obtained after abdominal attack and at least 1 week later in 36 patients with FMF compared with healthy and diseased controls. They found that there were 15 patients with Henoch–Schoenlein purpura (7%). The diagnosis of FMF was made after the onset of Henoch–Schoenlein purpura in nine. Occult blood was positive in the first stool specimens obtained after an attack in 17 of the 36 patients with FMF (47%). Nine out of 12 patients with Henoch–Schoenlein purpura and FMF skin biopsy

### Table 1 A summary of the reported FMF cases with Henoch–Schoenlein purpura

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Henoch–Schoenlein purpura patients (total FMF patients)</th>
<th>Skin biopsy</th>
<th>Kidney, biopsies</th>
<th>Findings, deposits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotem et al. 1962 [16]</td>
<td>7 (ND)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sohar et al. 1967 [17]</td>
<td>17 (470)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Flatou et al. 1982 [18]</td>
<td>8 (50)</td>
<td>4</td>
<td>2</td>
<td>C3</td>
</tr>
<tr>
<td>Schlesinger et al. 1983 [29]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>IgM, C3</td>
</tr>
<tr>
<td>Tunca et al. 2005 [32]</td>
<td>75 (2838)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Balbir et al. 2007 [31]</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Leucocytoclastic vasculitis</td>
</tr>
<tr>
<td>Nikavar et al. 2008 [33]</td>
<td>1</td>
<td>—</td>
<td>1</td>
<td>Crescentic glomerulonephritis</td>
</tr>
</tbody>
</table>

ND: no data.
showed a leukocytoclastic vasculitis. No mention was made regarding the presence or absence of IgA deposits. Nevertheless, in three out of five such patients' serum IgA was elevated. In this study the authors did not find a more severe course of Henoch–Schoenlein purpura disease in FMF patients. However, the ages at FMF diagnosis were significantly younger in the FMF–Henoch–Schoenlein purpura group than in the controls who had only FMF.

In 2007 Balbir et al. [31] described a family in whom two siblings with FMF developed Henoch–Schoenlein purpura. In both of them skin biopsy revealed leukocytoclastic vasculitis with no claim about IgA deposits.

In a Turkish FMF series published by Tunca et al. [32] there were only 2.7% of patients with Henoch–Schoenlein purpura. No data were available regarding skin or renal biopsies taken from these patients. In this cohort, the number of males with FMF and Henoch–Schoenlein purpura was twice that of the females. Nickavar and Ehsanipour [33] also published a case of FMF patients with Henoch–Schoenlein purpura where renal biopsy disclosed crescentic glomerulonephritis without IgA deposits.

Comorbidity or integral feature of FMF?

Based upon the above data the question raised is whether these vasculitic rashes which occur in FMF patients do really reflect Henoch–Schoenlein purpura comorbidity or whether these are uncommon features of what we call FMF today.

Since in most reports data about IgA deposits in skin or renal biopsies are lacking and in the few cases where the deposits were identified they were not of the IgA type, in retrospect a firm diagnosis of Henoch–Schoenlein purpura comorbidity is quite difficult. A more plausible explanation is that the vasculitic rash is an additional, albeit rare, manifestation of FMF. This idea is not unreasonable since a similar possible explanation was suggested with regards to the combination of PAN and FMF. Over the years reports of patients with FMF and PAN have increased [15, 34]. Analysis of these studies revealed that patients with PAN and FMF tend to be much younger when compared with classic PAN patients. Perirenal haematoma seems to be a rather distinctive feature in FMF–PAN patients since about 50% of the patients developed peri-renal haematomas prior to or at diagnosis. Another distinctive feature of these patients is severe myalgia, which raises a difficult differential diagnosis with protracted febrile myalgia (PFM). Survival was significantly better in FMF–PAN patients than expected for other classical isolated PAN patients, for whom the 5-year survival rate is 58–80% [35]. These data support the clinical impression about a favourable outcome of PAN and FMF.

Interestingly, anti-streptolysin O was elevated in all FMF–PAN patients tested. Streptococcal infections are still prevalent in the region, and this association may be coincidental. However, streptococcal infections have been implicated in PAN, especially in young patients [36, 37]. Superantigens of streptococci have been implicated in experimental models of vasculitis and may participate in the inflammatory cascade in human vasculitis as well. On the other hand, hepatitis B antigen was not as frequent as might have been expected in patients with isolated PAN. Thus, it is tempting to suggest that the PAN-vasculitis in FMF patients might be another feature of the disease which can be triggered by Strep infection and thus different in course and prognosis from the typical and classical PAN.

Another such example is the co-presentation of SpA in FMF patients. Dilsen [38] was the first to describe the co-existence of SpA and FMF. However, Langevitz et al. [39] studied this association in a large cohort of FMF patient and found features consistent with ankylosing spondylitis in only 0.3% of them. These authors suggested that SpA should be included in the musculoskeletal manifestations of FMF. Recent reports echoed this initial observation describing SpA manifestations in FMF, mostly sacroilitis in patients who had chronic musculoskeletal symptoms [40, 41]. In a study by Eshed et al. [42] ankle enthesopathy was found frequently in FMF patients with exertional leg pain suggesting that this unique manifestation of FMF should be included within the spectrum of SpA. Importantly, the authors observed that exertional leg pain was not only a prevalent finding in FMF patients but was also a marker of more severe disease. Patients with exertional leg pain were younger at disease onset, had more attacks per year and had more frequent involvement of multiple sites. A family history of FMF was more prevalent among the study group, and the M694V mutation, which is associated with a more ominous prognosis in FMF, was more common in patients with exertional leg pain. The majority (73.5%) of patients with exertional leg pain exhibited features of enthesopathy on ankle MRI, including enthesitis of the Achilles tendon and plantar fascia as well as bone marrow oedema and excessive synovial fluid, compared with only one-third of the controls.

Thus in addition to the above observations regarding the clinical differences between PAN or SpA associated with FMF compared with the classical isolated PAN or ankylosing spondylitis, Henoch–Schoenlein purpura combined with FMF also differ from typical Henoch–Schoenlein purpura alone. In the former, Henoch–Schoenlein purpura tends to re-occur several times in the same patient (as the case with FMF attacks) [11, 17, 18, 30]. The age at diagnosis of FMF in patients with Henoch–Schoenlein purpura was much younger (12.5 ± 0.6 vs 19.7 ± 0.8) [30]. The skin rash may affect the face and the trunk in the FMF patient, features which are not typical in isolated Henoch–Schoenlein purpura. In the combined appearance of Henoch–Schoenlein purpura and FMF, in the very few cases where IgA studies were available these did not show IgA deposits. Moreover the usual histology of these specimens was leukocytoclastic vasculitis. Finally, supporting this view is the finding that in most cases with these clinical features (Henoch–Schoenlein purpura, PAN and sacroilitis associated with FMF) the patients carried one or two M694V MEFV mutations that may predispose them to these
uncommon manifestations as they do in cases of PFM [43]. The fact that several studies demonstrated high prevalence of MEVF mutations in Henoch–Schönlein purpura and SpA patients may suggest that they may contribute to the pathogenesis of these diseases. On the other hand it may support the notion that these clinical features (Henoch–Schönlein purpura and SpA) may be an integral feature of FMF as well [44–46].

In at least 8% of all patients with RA there is some degree of sacroiliitis. In these cases we never attempt merging both diseases, which were split in the early 1960s. One should remember that many clinical conditions are construct diseases and we have a tendency to lump a new clinical feature we see immediately into a previously defined category. It seems that there is a place for a different approach in which we should consider the new (albeit uncommon) clinical manifestation as an integral feature of the disease, the construct, rather than raising the possibility of coexistence of two different disease entities.

This view of new clinical manifestations of FMF—vasculitic rash mimicking Henoch–Schönlein purpura, PAN—like vasculitis and ankle enthesopathy [47] raises again the problematic issue of the name familial Mediterranean fever. FMF traditionally was defined as a periodic disease presented with fever and serositis. Over the years we learned that the disease may have wider clinical features. Moreover, the MEVF mutations that are usually associated with FMF may sometimes be associated with quite different syndromes and clinical entities [48]. These observations and findings may justify again the need for reconsidering the nomenclature of the periodic fever syndromes and especially FMF. It seems that MEVF or pyrin associated disease may be a better and more accurate name in these cases [49].

Conclusion

In summary we propose that the common wisdom of interpreting all skin vasculitis seen in a patient with FMF as Henoch–Schönlein purpura should be re-examined. It seems clear that we need to particularly know whether there are IgA deposits in these vasculitic lesions before we come to a more justified conclusion. Until then, it seems that an alternative explanation for the coexistence of these diseases. On the other hand it may support the notion that these clinical features (Henoch–Schönlein purpura and SpA) may be an integral feature of FMF as well [44–46].

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