Henoch-Schönlein purpura associated with acetaminophen and codeine

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Abstract. We report a case of a relapse of Henoch-Schönlein Purpura (HSP) associated with intake of paracetamol (also known as acetaminophene) and codeine. A 69-year-old man presented with fever, gross hematuria, acute renal failure, palpable purpuric skin rash over the legs, feet and arms, arthralgias and abdominal discomfort. 1 week before he had started therapy with co-efferalgan (association of paracetamol and codeine) for cervical arthrosis. Blood test revealed increase in serum creatinine levels (2.6 mg/dl), CRP (375 mg/dl), with no thrombocytopenia or hypocomplementemia. Co-efferalgan was discontinued. Gross hematuria resolved in 2 days, purpuric rash disappeared in 10 days, renal function returned to normal after 2 weeks and abdominal pain and arthralgias improved on the following 2 – 3 weeks. An objective causality assessment in accordance with the Naranjo algorithm, revealed that the adverse drug reaction was probable between paracetamol/codeine and Henoch-Schönlein purpura. To our knowledge, and based on a medline search (up to 2005), we believe that this could be considered the first case of Henoch-Schönlein purpura, associated with intake of paracetamol and codeine. Although this event could be considered rare, clinicians should to be aware of possible associations between HUS and the intake of paracetamol and/or codeine to provide an early therapeutic intervention and a close monitoring.

Introduction

Henoch-Schönlein Purpura is a systemic vasculitis characterized clinically by palpable purpura, arthritis with renal and gastrointestinal involvement and, histologically, by immunodeposition of IgA-containing immune complexes in the skin or kidney. Such disease is more common in children with an incidence of 15/20 cases/100,000 children per year [Nielsen 1988]. In adults, the incidence of renal involvement ranges from 45 – 85% of cases [Coppo et al. 1999]. There is some debate regarding the different clinical course between adults and children. Indeed, a study showed that clinical presentation, renal lesions and long-term outcome were the same among adult and pediatric patients with HSP and renal involvement [Coppo et al. 1999], while, another study, which observed retrospectively 250 adults on an average of 14.8 years, showed that clinical presentation in adults was more severe and the outcome was poorer than in children [Pillebout et al. 2002].

Pathogenesis is still unknown, however, an infection involving the mucosal system of the upper respiratory tract has been reported as a likely cause of the illness [Miura et al. 1992]. Another possible cause is the association with drug ingestion [Borras-Blasco et al. 2003]. Here, we present a case of an adult patient who developed a drug-related Henoch-Schönlein purpura.

Case report

In August 2004, a 69-year-old man was admitted to our hospital with microscopic hematuria, proteinuria and acute renal failure. 2 months before admission he was diagnosed with purpuric rash with an unconfirmed association with drug ingestion (ketorolac-trometamline). The patient stated he had taken several drugs, and the onset of purpuric rash had occurred a few days after ingesting ketorolac. At that time, urine analysis showed microscopic hematuria with normal renal function. The purpuric rash did not disappear on withdrawal of ketorolac. On admission, physical examination revealed persistence of multiple confluent purpuric lesion on the legs,
Table 1. List of HSP drug-related.

<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>Drug</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>de Vega T</td>
<td>Clarithromycin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>2</td>
<td>Zillicx AP</td>
<td>Streptokinase</td>
<td>Trombolytic</td>
</tr>
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<td>3</td>
<td>Valero Prieto I</td>
<td>Spiramycin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>4</td>
<td>Garnb A</td>
<td>Ciprofloxacin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>5</td>
<td>Escudero A</td>
<td>Cefuroxime</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>6</td>
<td>Prajapati C</td>
<td>Ranitidine</td>
<td>Gastric保护</td>
</tr>
<tr>
<td>7</td>
<td>Alberich RS</td>
<td>Acetylsalisylic Acid</td>
<td>Antiinmobil</td>
</tr>
<tr>
<td>8</td>
<td>Michail S</td>
<td>Vancomycin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>9</td>
<td>Goncalves R</td>
<td>Enalapril</td>
<td>Anti-hypertensive</td>
</tr>
<tr>
<td>10</td>
<td>Bosch X</td>
<td>Losartan</td>
<td>Anti-hypertensive</td>
</tr>
<tr>
<td>11</td>
<td>Goldberg E</td>
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<td>Antibiotic</td>
</tr>
<tr>
<td>12</td>
<td>Goad JA</td>
<td>Metoclopramide</td>
<td>Gastrointestinal motility modulator</td>
</tr>
<tr>
<td>13</td>
<td>Pons R</td>
<td>Ciprofloxacin</td>
<td>Antibiotic</td>
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<tr>
<td>14</td>
<td>Choi SJ</td>
<td>Thalidomide</td>
<td>Immune response modulator</td>
</tr>
<tr>
<td>15</td>
<td>Borras-Blasco J</td>
<td>Clarithromycin</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>16</td>
<td>Borras-Blasco J</td>
<td>Acenocoumarol</td>
<td>Anticoagulant</td>
</tr>
</tbody>
</table>

abdominal pain with nausea and arthralgias. The patient had lost 5 kg in a month. Laboratory results were creatinine 1.3 mg/dl, hematocrit 33%, white blood cell count 12,110/mm³ (N 82%), platelet count 356,000/mm³, 24-hour proteinuria 0.86 g. Urine sediment showed microscopic hematuria (80% dysmorphic erythrocytes). C-reactive protein level was 46 mg/l. Serum IgA, IgG, IgM were normal. Serum complement was normal. Cryoglobulins, antinuclear antibodies, antineutrophilic cytoplasmic antibodies (cytoplasmic pattern), antineutrophilic cytoplasmic antibodies (perinuclear pattern) were all normal or negative. Serologic tests for hepatitis B and C were negative. Colon endoscopy showed aspecific colitis, colon biopsy revealed a mild chronic inflammatory infiltrate. Abdominal ultrasound disclosed normal kidneys. Renal biopsy confirmed a diagnosis of IgA nephropathy with increased and hypercellular mesangial areas and mesangial deposition of IgA and C3 on immunofluorescence. In addition, there were cellular crescents in 3 glomeruli.

In such a clinical setting, the immune complex process is indicative of Henoch-Schönlein purpura nephritis. The patient was treated with boluses of methylprednisone (750 mg) for 3 days followed by a combination of prednisone (0.5 mg/kg/day) and cyclophosphamide (125 mg/day). 1 year later, due to cervical arthrosis, he started therapy with coefferalgan (1.5 g/day of acetaminophen and 90 mg/day of codeine phosphate). After 1 week, the patient presented with gross hematuria, arthralgias in the knees, wrists and elbows, and extensive bilaterally petechial hemorrhages on the arms and legs. On admission, temperature was 39.5 °C and blood pressure was normal. Laboratory testing revealed creatinine 2.7 mg/dl, hematocrit 30.5%, white blood cell count 13,510/mm³ (N 87%), platelet count 257,000/mm³, 24-hour proteinuria 0.95 g. Urine sediment showed macroscopic hematuria (severe dysmorphic erythrocytes). C-reactive protein level was 375 mg/l. Serum IgA, IgG, IgM were normal. Serum complement was normal. Antinuclear antibodies were negative. Antineutrophilic cytoplasmic antibodies (cytoplasmic pattern), antineutrophilic cytoplasmic antibodies (perinuclear pattern) and anti-DNA antibodies were negative. Cryoglobulins were negative. Co-efferalgan was discontinued. Gross hematuria and the purpuric rash disappeared and renal function returned to normal after 2 weeks. On the last examination, 9 months later; serum creatinine was 0.9 mg/dl and proteinuria was 0.125 g/24h.

Discussion

The involvement of renal disease in HSP may vary [Cameron 1984]. Most patients may
Henoch-Schönlein purpura drug-related

have renal disease characterized by hematuria and proteinuria, with slightly elevated serum creatinine. However, in some patients, nephritic syndrome and/or acute renal failure may occur [Blanco et al. 1997]. Clinical remission is not common in patients with HSP and, as Pillebout observed, it was achieved in only 20% out of 250 adult patients [Pillebout et al. 2002]. Factors associated with a poor prognosis, like high degree of proteinuria, renal failure, high percentage of sclerotic glomeruli, fibrinoid necrosis and interstitial fibrosis were mildly present in our patient.

Several drugs are associated with onset of HSP. In Table 1, HSPs associated with drugs ingestion are listed. Since most drugs are antibiotics, we could also deduce that infection may play a role in the pathogenesis of HSP in these cases. Other drugs include antihypertensive such as enalapril or losartan, metoclopramide, ranitidine, streptokinase, acetylsalicylic acid, acenocoumarol and thalidomide.

In 1987, a case of HSP associated with Co-dydramol (acetaminophen plus dihydrocodeine tartrate) ingestion was reported [Naranjo et al. 1981]. From a careful reading of this case report we deduced that the diagnosis of HSP could be questioned. Indeed, the symptoms of the patient, in Richards and colleagues' case report, were characterized by purpuric rash on the feet, legs, abdomen and arms, joint pains and ankle and foot edema, without carrying out immunofluorescence studies [Richards and Linley 1987].

IgA immunodeposition, either in the skin or kidney, is necessary for HSP diagnosis [Cameron 1984]. In addition to IgA immunodeposition, their patient didn't show any clear sign of renal involvement, since there was no evidence of hematuria, proteinuria or renal failure, and the only evidence of renal disease was the presence of edema. Considering all these factors, other diagnoses could have been made such as hypersensitivity vasculitis, mixed essential cryoglobulinemia, microscopic polyangiitis, acute post-streptococcal glomerulonephritis and endovascular infection [Michel et al. 1992, Richards and Linley 1987].

The different renal involvement in the 2 episodes is relevant. Indeed, in the first episode, renal failure was mild and only microhematuria was observed, whilst the relapse was characterized by rapidly progressive glomerulonephritis with gross hematuria. In the last episode, the evolution towards end-stage renal disease was arrested due to discontinuation of drug (acetaminophen/codeine) intake.

The occurrence of HSP was probably related to the consumption of acetaminophen and codeine for many reasons, even if another pathogenetic mechanism cannot be ruled out. First of all, there was a close temporal relationship between drug ingestion and onset of symptoms. Moreover, co-efferalgan (acetaminophen and codeine) was the only drug added before the onset of cutaneous, renal and joint symptoms, and when its intake was interrupted, the patient's general condition improved. For this reason, in accordance with our data and on the basis of the Naranjo algorithm, adverse drug reaction could be considered possible [Habib et al. 1993].

It has to be mentioned that our patient had taken acetaminophen several times in the past, whilst he denied he had taken codeine in the past. Therefore, we deduced that codeine intake, or the combination of both molecules, may be responsible for adverse drug reaction. Drug rechallenge was not attempted for ethical reasons, since, with the available data, adverse drug reaction could be considered possible.

For this reason, we believe that our patient may represent the first clear evidence of a possible relation between HSP and acetaminophen/codeine consumption.

Clinicians should be aware of possible associations between HSP and acetaminophen and/or codeine consumption in order to provide prompt therapeutic intervention, including drug intake discontinuation.

References


