Gastrointestinal Henoch–Schönlein purpura successfully treated with Mycophenolate Mofetil

Description of 2 case reports

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Abstract

Rationale: Henoch–Schönlein Purpura (HSP) is an acute small vessel vasculitis. It is the most common vasculitis in children. In majority of the cases, the disease is self-limited. Relapses can occur, in particular during the first year of the disease. There is no consensus on a specific treatment. The efficacy and safety of steroidal treatment in treating HSP is still controversial. Immunosuppressive treatment of HSP nephritis is used in patients with severe renal involvement (nephrotic range proteinuria and/or progressive renal impairment). The literature on immunosuppressive treatment of severe HSP without kidney involvement is scanty.

Patients concerns: We report 2 case reports of 2 adolescents affected from Henoch–Schönlein Purpura and severe gastrointestinal involvement. Both patients presented a poor response to steroids treatment.

Diagnoses: The diagnosis of HSP was made according to the diagnostic criteria published by European League against Rheumatism and Pediatric Rheumatology European Society in 2006

Interventions: In consideration of the recurrence of the Henoch Schönlein Purpura and the gastrointestinal involvement, we decided to start Mycophenolate Mofetil treatment.

Outcomes: In both patients all clinical manifestations resolved in few days.

Lessons: In our cases of HSP with gastrointestinal involvement Mycophenolate Mofetil treatment has been very effective. This experience teaches us that immunosuppressive agents may be very useful to induce and maintain remission not only in renal involvement, but in all cases of persistent, recurrent, or complicated Henoch Schönlein Purpura in children.

Abbreviations: ANA = anti-nuclear antibodies, ANCA = anti-neutrophil cytoplasmic antibodies, ASO = anti-streptolysin O, CRP = C-reactive protein, CSA = cyclosporine A, DS-DNA = anti-double-stranded-DNA, EGDS = esophagogastroduodenoscopy, ENA = extractable nuclear antigens, ESR = erythrocyte sedimentation rate, GCS = glucocorticosteroids, HSP = Henoch–Schönlein Henoch Purpura, IV = in vein, MMF = mycophenolate mofetile, MPA = mycophenolic acid, NSAIDs = nonsteroidal anti-inflammatory drugs, PO = per os, RF = rheumatoid factor.

Keywords: abdominal pain, gastrointestinal bleeding, mycophenolate mofetile, purpura, Schönlein–Henoch syndrome

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As this is a case report, the approval of the ethics committee is not required, but the parental consent that has been obtained.

Written consent for publication has been obtained from the parents of both patients.

Availability of data and material: Medical records.

The authors have no conflicts of interest to disclose.

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1. Introduction

Henoch–Schönlein Purpura (HSP) is the most common systemic vasculitis in children. The majority of patients are under 10 years old. The annual incidence of HSP in children is estimated to be 15,000 cases. The proportion of males and females in children is close to 2:1. Diagnostic criteria were published by the European League against Rheumatism and the Pediatric Rheumatology European Society. They include palpable purpura in combination with at least one of the following manifestations: gastrointestinal involvement, immunoglobulin A deposition in biopsy, arthritis or arthralgia, and renal involvement (Table 1). Clinical manifestations are: palpable purpura (96%), arthralgia/ arthritis (64%), abdominal pain (66%), gastrointestinal bleeding (28%), renal involvement (39%), subcutaneous edema (42%), and orchitis (5%). Patients rarely show severe pulmonary hemorrhage (1%), or cerebral vasculitis (2%). Purpuric rash is the most typical manifestation. Although recurrence is common among children (recurrence rate, 2.7%–66.2%), HSP prognosis is generally good. Significant morbidity and mortality are associated with gastrointestinal tract lesions and nephritis. The development of renal disease within the first 6 months after disease’s onset or recurrent relapses associated with nephropathy suggest a poor prognosis for renal function. Additional poor prognosis factors are gastrointestinal bleeding, decreased factor XIII activity, hypertension, renal failure at onset. Treatment is supportive, with maintenance of good hydration, and with control of pain with analgesics. However, the efficacy and safety of the therapy with steroids and immunosuppressant drugs in treating HSP is still controversial. There are retrospective studies and case reports that suggest effective use of corticosteroids for the treatment of abdominal pain, renal involvement, and severe orchitis. Immunosuppressive treatment of HSP nephritis is used in patients with severe renal involvement (nephrotic range proteinuria and/or progressive renal impairment). The literature on immunosuppressive treatment of severe HSP without kidney involvement is scanty. In this article we report the successful use of MMF in 2 patients affected by HSP with gastrointestinal involvement.

2. Case reports

2.1. Case number 1

At the age of 8 years, after a streptococcal pharyngitis treated with amoxicillin, patient presented pain in her lower limbs, difficult to walk and purpuric lesions to the limbs. During hospitalization in a local hospital she was treated with oral prednisone, 2 mg/kg/die. She was discharged for disappearance of symptoms after 1 week with diagnosis of suspected vasculitis and therapy with prednisone (2 mg/kg/die) for 10 days. After 3 years of good conditions, patient presented hematemesis and purpuric lesions so she was hospitalized again. Laboratory tests were unremarkable for: complete blood count, kidney and liver parameters, electrolytes and coagulation test, antinuclear antibodies (ANA) celiac screening. Throat swab was negative. Urinalysis did not show neither proteinuria nor hematuria. Occult blood was present in the stool. Abdomen ultrasound was normal. Methylprednisolone in vein (2 mg/kg/die for 3 days) was administered, then oral prednisone (2 mg/kg/die) was prescribed. She was discharged after 10 days with Schönlein Henoch Vasculitis diagnosis. Oral prednisone was suspended after 10 days.

Four years later patient presented again purpuric lesions and hematemesis, so she was hospitalized. Patient underwent both to an esophagogastroduodenoscopy (EGDS) that was negative and to a skin biopsy, suggestive of leukocytoclastic vasculitis with IgA deposition, typical of HSP. HSP diagnosis was confirmed and oral prednisone (2 mg/kg/die, gradually tapered in a month) was prescribed, with an initial improvement of symptoms. At steroids reduction purpuric lesions, hematemesis, abdominal pain, and diarrhea came back again, so patient came to Rheumatology Unit of our Department for the first time. On the examination she presented diffuse purpuric lesions and abdominal pain. No arthritis was detected. Her blood tests were unremarkable for: complete blood count, liver and kidney function, ANA, extractable nuclear antigens (ENA), Anti neutrophil Cytoplasmic antibodies (ANCA), rheumatoid factor (RF), anti-double-stranded DNA (dsDNA), Anti-streptolysin O (ASO), immunoglobulins, complement C3 and C4. Factor XIII activity was reduced (65%, normal value > 75%). Inflammatory parameters were slightly increased: erythrocyte sedimentation rate (ERS) 2.5 mm/h (normal value < 15 mm/h), C-reactive protein (CRP) 1 mg/dL (normal value < 0.8 mg/dL). Urinalysis was normal. Occult blood in the stool was present. Throat swab was negative. Abdomen ultrasound showed bowel wall thickening. Cardiac ultrasound was normal. Therapy with oral prednisone 25 mg in the morning and 20 mg in the evening was prescribed, with initial improvement of symptoms, but after a few days she presented new purpuric lesions on knees and feet, and abdominal pain. Due to the recurrence of her symptoms and the lack of a sustained response to steroids, we decided to start MMF treatment. Patient was treated with MMF (600 mg/m² twice a day) for a month, in the same period of time prednisone was gradually reduced. All clinical manifestations resolved in 2 weeks. After the first month of treatment, MMF was gradually reduced for a period of 6 months with a complete regression of symptoms.

Table 1

| Definition | Purpura palpable or petechiae, in particular on lower limbs, not related to thrombocytopenia |
|-----------|---------------------------------------------------------------|
| Purpura (mandatory) | At least 1 of the following: Abdominal pain, Histopathology, Arthritis or arthralgia, Renal involvement |

The EULAR/PRINTO/PRES criteria for HSP, Ann Rheum Dis 2010.21
vasculitic lesions and abdominal symptoms. There was no evidence of relapse in a 6 months follow-up.

2.2. Case number 2

After an upper respiratory tract infection, a 13-year-old boy presented purpuric lesions on upper and lower limbs with spontaneous resolution in 3 days. After a week patient presented again purpuric lesions on the limbs and trunk associated with abdominal pain so he was brought to emergency department. The abdominal ultrasound was normal and urinalysis revealed mild proteinuria, but no treatment was prescribed. Due to the persistence of purpuric lesions, abdominal pain, and the onset of vomiting and gastrointestinal bleeding, the patient was hospitalized to our Department. On examination purpuric lesions on limbs and trunk were detected, patient referred both abdominal and testis pain. No signs of arthritis were found. Blood tests were unremarkable for: complete blood count, liver and kidney function, ERS, CRP, ANA, ENA, ANCA, RF, dsDNA, ASO, immunoglobulins, complement C3 and C4. Factor XIII activity was reduced (55%, normal value > 75%). Virological screening revealed Influenza Virus. Urinalysis showed mild proteinuria. Throat swab was negative. Abdomen ultrasound showed bowel wall thickening, while tests ultrasound was normal. HSP diagnosis was confirmed. Methylprednisolone iv (2 mg/kg/die) was administered for 3 days, then oral prednisone (2 mg/kg/die) was prescribed, with resolution of symptoms. After a few days patient presented new purpuric lesions at the limbs and trunk and abdominal pain. Considering the recurrence of symptoms, the abdominal involvement, and the lack of a sustained response to steroids, MMF (600 mg/m²/d) was added to the therapy, and prednisone was gradually reduced over the course of month. Symptoms improved few days after starting to treat the patient with MMF. MMF treatment was continued for a month, and gradually reduced over 6 months, with regression of both purpuric lesions and abdominal pain. There was no evidence of relapse in a 6 months follow-up.

3. Discussion

We described 2 cases of patients affected by recurrent HSP with gastrointestinal involvement successfully treated with MMF. Gastrointestinal involvement is one of the most debilitating symptoms of HSP, which may prompt symptoms ranging from abdominal pain, vomiting, intussusception to gastrointestinal hemorrhage.[14] Our patients presented abdominal pain and gastrointestinal bleeding. It has been reported that some patients with steroid-resistant gastrointestinal involvement may benefit from immunosuppressive treatment such as cyclophosphamide or MMF.[14,15] MMF suppressing lymphocyte proliferation is very effectiveness in many autoimmune disorders even at pediatric age, such as lupus erythematous systemic.[16,17] Recent studies suggest that mycophenolatic acid (MPA), the active metabolite of MMF, can inhibit the adhesion of leukocytes to endothelial cells, which is a key process in the pathogenesis of ANCA vasculitis.[18] Therefore, MMF is used in children with HSP, successfully treated with MMF. Wang et al[20] in a recent observational study reported the effective use of MMF in 18 patients affected by HSP with gastrointestinal involvement unresponsive to systemic steroids.

Our patients presented a severe gastrointestinal involvement partially responsive to high dose of steroids, so we decided to start an immunosuppressive treatment with MMF. Adverse effects of MMF are less severe than other immunosuppressive drugs or steroids.[14,21] (Table 2). In children a long exposure to steroids could induce also growth impairment.[21] After the beginning of MMF both vasculitis lesions and abdominal symptoms disappeared in few days. Neither of our patients developed side effects due to MMF. According to literature data[13,14,20] and to our experience MMF seems to be a safe and effective medication to treat HSP. This drug could be used in case of recurrence.
of steroids side effects, steroids dependency (2 relapses during steroid tapering), or steroids inefficacy.\cite{13,20} There are no official guidelines about how long MMF should be administered in HSP with gastrointestinal involvement. However, following a recent guidelines about how long MMF should be administered in HSP with gastrointestinal involvement.

4. Conclusions

The report of these 2 cases suggests that MMF may be a promising therapeutic alternative to induce and maintain remission of recurrent HSP with gastrointestinal involvement. Our patients did not have adverse events associated with MMF therapy. Further research and multicenter clinical trials with long-term follow-up to confirm the efficacy of MMF in the treatment of HSP with gastrointestinal involvement are warranted to consolidate information about the effectiveness of MMF in treating HSP with gastrointestinal involvement.

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Author contributions

GMF conceived the paper, involvement in the diagnosis and management of patient, analyzed and interpreted the patient data, writer of paper and revision of bibliography; ID, CG, MDGE, and OAN supervision of the medical procedures, including the decision of the use of MMF, writer of paper. All authors read and approved the final manuscript.

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