Unexpected outcome (positive or negative) including adverse drug reactions

Cyclosporine-induced haemolytic anaemia in a child with juvenile dermatomyositis

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Summary

Cyclosporine-induced haemolysis is a very rare adverse reaction. The few published cases in the literature are described in the context of haemolytic-uraemic syndrome in transplanted patients. We report a case of cyclosporine-induced haemolytic anaemia in a 9-year-old girl being treated for severe dermatomyositis.

BACKGROUND

We decided to write the case to report a rare paediatric case of cyclosporine-induced haemolytic anaemia in the context of rheumatological disease. This case highlights the difficult aetiological diagnosis of acute anaemia associated with rheumatological disease, highlighting the high index of suspicion needed to diagnose drug-related causes.

CASE PRESENTATION

A previously healthy 9-year-old afro-descendent girl presented in the emergency department (ER) with polyarthralgia and polymyalgia causing progressive functional impairment over a 3-week period. In days preceding the ER visit low-grade fever, dysphonia and dysphagia were noted. The laboratory results revealed an elevated lactate dehydrogenase (700 IU/l), aspartate aminotransferase (301 U/l), erythrocyte sedimentation rate (78 mm/h) and creatine kinase (4959 IU/l). She was admitted with suspected viral myositis and started treatment with ibuprofen. During the admission generalised cutaneous oedema, malar and heliotrope rash as well as a hyperpigmented cutaneous lesion with palpable subcutaneous calcifications (confirmed by x-ray) were observed. The septic screen was negative and the autoimmune panel revealed high-antinuclear antibody titers (1/640–Sp100+). The muscle biopsy was compatible with dermatomyositis.

Owing to the progression of symptoms (worsening dysphonia/dysphagia and severe motor impairment), we started immunosuppressive therapy with methotrexate, prednisolone and cyclosporine.

On the seventh day of treatment, a routine laboratory panel revealed acute haemolytic anaemia (haemoglobin 6.5 g/dl; reticulocyte count 230 000/mm³–10, 6%; bilirubin 2.09 mg/dl and immeasurable haptoglobin level). There was no visible blood loss and a faecal occult blood test was negative. Haemoglobin electrophoresis and G6PD activity were normal. Direct and indirect Coombs as well as cold agglutinin tests, screening for HIV1, HIV2, hepatitis B virus (HBV) and syphilis were all negative. The serological tests for Adenovirus, Parainfluenza, Influenza, *Mycoplasma pneumoniae*, Chlamydia and Parvovirus B19 were also negative. The serological tests for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were positive for remote infection. The cyclosporine-incubated-Coombs test was positive.

After methylprednisolone pulse therapy, cyclosporine withdrawal along with azathioprine introduction resulted in elevation of serum haemoglobin as well as cessation of haemolysis (table 1).

INVESTIGATIONS

- ▶ Haemoglobin electrophoresis
- ▶ G6PD enzyme activity

Table 1 Results of blood tests taken at baseline and times post-therapy

Time post-therapy	Baseline	D7	D9	D13	D17	D20	D27	D34
Haemoglobin (g/dl) (11.5–15.5)	11.6	7.0	6.5	6.6	8.5	9.4	9.3	10.1
Absolute reticulocyte count $\times 10^9/l$ (22–139)	N/A	155.6	170.2	230	178.6	190.4	99.7	97
Reticulocytes, (%) (0.5–2.5)	N/A	6.2	7.7	10.6	6.2	6.0	3.2	2.9
Total bilirubin, (μ mol/l) (<20.5)	13.2	26	35.7	24.6	22.1	23.6	9.9	9.9
Conjugated bilirubin, (μ mol/l) (<3.4)	10.9	11.4	13.7	5.5	9.6	11.0	4.1	5.3

N/A, not available.

Urinalysis at D7 was normal.

Repeatedly normal values of creatinine and urea.

Results shown in bold are outside the reference range.

Methylprednisolone pulses at D10–D12.

Cyclosporine withdrawal at D19.

- Direct and indirect Coombs test
- Cold agglutinins test
- Drug-incubated Coombs test
- Viral serologic tests (EBV, CMV, Parvovirus B19, HBV, HIV1, HIV2, Adenovirus, Parainfluenza, Influenza)
- Chlamydia, Mycoplasma and Treponema serological tests

DIFFERENTIAL DIAGNOSIS

- Haemoglobin disease
- G6PD deficiency
- Autoimmune haemolytic anaemia
- Drug-related haemolytic anaemia
- Infection-induced haemolytic anaemia

TREATMENT

- Methylprednisolone pulse therapy
- Cyclosporine withdrawal
- Azathioprine introduction

OUTCOME AND FOLLOW-UP

The patient improved and is on regular follow-up of her baseline condition.

DISCUSSION

Anaemia in the context of rheumatological disease has many possible causes, including chronic disease anaemia, acute/chronic blood loss (non-steroidal anti-inflammatory drug-induced upper GI bleeding), autoimmune haemolytic anaemia and haemophagocytic syndrome.

In this particular case, haemolytic anaemia was initially diagnosed. Autoimmune-related causes, a baseline condition in which acute disease can trigger haemolysis and drug-induced haemolysis were also possibilities. Owing to the patient's African origin, the most frequent haemoglobinopathies and red blood cell enzymopathies were excluded.

Direct and indirect Coombs tests were negative. We observed a temporal relationship between the treatment with immunosuppressive drugs and the onset of haemolytic anaemia. Thus, a drug-incubated Coombs test was ordered and revealed itself positive for cyclosporine.

An improvement was noted after cyclosporine cessation and treatment with azathioprine was started.

Cyclosporine is an immunosuppressive agent used in various conditions such as prevention of allograft rejection in transplant recipient patients,¹ severe rheumatoid arthritis,² psoriasis³ and Crohn's disease.⁴

Microangiopathic haemolytic anaemia is a very rare adverse side effect described in the literature, following solid organ transplantation. Normally pathological and clinical findings are consistent with haemolytic uremic syndrome. Both early⁵ and late⁶ onset of this condition can lead to graft loss.^{5–10} There are few cases of cyclosporine induced haemolytic anaemia in the context of

rheumatological disease cited in the literature.¹¹ This is to the best of our knowledge the first paediatric case described.

We report this interesting case as a reminder that adverse effects of drugs must remain on the list of causes of anaemia, in paediatric rheumatological disease, considering the expanding drug formulary in this age range.

Learning points

- A paediatric case of cyclosporine-induced haemolytic anaemia is reported.
- It can occur in the absence of haemolytic-uraemic syndrome.
- High index of suspicion is needed to diagnose drug-related causes of haemolytic anaemia especially when other causes appear more probable.
- In this case the diagnosis was confirmed by a positive cyclosporine incubated drug combs test as well as marked improvement in the patient after its interruption.

Competing interests None.

Patient consent Obtained.

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