LESSON OF THE MONTH

Gold treatment, nephrotic syndrome, and multi-organ failure in a patient with adult onset Still's disease

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A 25 year old Bengali woman presented acutely with a symmetrical inflammatory polyarthritis affecting knees, wrists, metacarpophalangeal (MCP) joints, and proximal interphalangeal (PIP) joints which had developed over six weeks. The distal interphalangeal joints were spared. She had a pigmented, scaly rash over the hands, chest, and back. There had been no fever, hair loss, mouth ulcers, genitourinary symptoms, Raynaud's phenomenon, and no significant past medical history. At presentation there was no lymphadenopathy or organomegaly. Initial investigations showed (normal range): haemoglobin 106 g/l (135-180 g/l), mean corpuscular volume 72.7 fl (76-96 fl), white cell count (WCC) $18 \times 10^9/l$ (neutrophilia) ($4-11 \times 10^9/l$), platelets $301 \times 10^9/l$ ($150-400 \times 10^9/l$), urea 6.2 mmol/l (3.0-8.3 mmol/l), creatinine 50 $\mu\text{mol/l}$ (44-133 $\mu\text{mol/l}$), alanine aminotransferase 71 IU (<50 IU), alkaline phosphatase 361 IU/l (20-130 IU), albumin 40 g/l (35-50 g/l), ferritin 1200 $\mu\text{g/l}$ (10-300 $\mu\text{g/l}$), plasma viscosity 2.1 mPa.s (1.50-1.72 mPa.s), C reactive protein (CRP) 230 mg/l (<5 mg/l), C3 and C4 levels normal, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor were negative. Blood cultures, hepatitis B and C serology, and the monospot test for glandular fever were negative. Radiographs of the hands showed soft tissue swelling around MCP and PIP joints, but were otherwise normal. A chest radiograph was normal. A differential diagnosis of seronegative rheumatoid arthritis and adult onset Still's disease (AOSD) was considered. Oral methotrexate 7.5 mg weekly, prednisolone 15 mg daily, and diclofenac 50 mg three times a day were started, with rapid clinical improvement and normalisation of liver function tests and inflammatory markers. After one month prednisolone was stopped.

Six months later, while taking oral methotrexate, her inflammatory arthritis relapsed in association with a fever of 39°C, malaise, a salmon pink non-pruritic macular rash over the trunk, and raised inflammatory markers. AOSD was diagnosed. Methotrexate was discontinued because of the presence of deranged liver function tests that were worse than at initial presentation. Prednisolone 15 mg a day was started. The fever and rash

settled, and liver function tests normalised; however, the inflammatory arthritis persisted and so intramuscular gold (Myocrisin) was started. A test dose of 10 mg was tolerated well. One week later 50 mg was given. Urine analysis was noted to be normal.

Two days later the patient developed a high swinging fever, confusion, and a recurrence of her characteristic rash when febrile. There was no organomegaly or lymphadenopathy. Investigations showed: haemoglobin 92 g/l, WCC $16 \times 10^9/l$ (neutrophilia), platelets $120 \times 10^9/l$, prothrombin time 26 seconds (16-18 s), partial thromboplastin time ratio 1.4 (0.8-1.2), cross link degradation products >32 $\mu\text{g/ml}$ (0.00-0.50 $\mu\text{g/ml}$), fibrinogen 1.3 g/l (1.5-4.0 g/l), creatinine 120 $\mu\text{mol/l}$, alanine aminotransferase 169 IU, alkaline phosphatase 150 IU/l, albumin 26 g/l, CRP 122 mg/l, plasma viscosity 2.01 mPa.s, C3 and C4 levels normal, ANA, ANCA, and rheumatoid factor negative, and chest radiograph normal. Proteinuria (3+) was noted on urine dipstick testing. A provisional diagnosis of septicaemia and disseminated intravascular coagulation (DIC) was made and treatment was started with broad spectrum antibiotics. Despite this, the DIC worsened and respiratory failure developed, requiring ventilation. Chest radiographs were consistent with adult respiratory distress syndrome. Because of a concern about macrophage activation syndrome (MAS), which has been reported as a complication of AOSD, a bone marrow aspirate was performed. However, characteristic changes of MAS were not found; the bone marrow was hypercellular, with no evidence of pathological haemophagocytosis.

Seven days after admission, and after repeated sterile blood cultures, intravenous methylprednisolone was given, at a dose of 1 g daily on three consecutive days, followed by oral prednisolone 30 mg daily. This led to a rapid clinical improvement. However, the patient remained hypoalbuminaemic (albumin 22 g/l) with a urinary protein excretion of 11.5 g/24 h (<0.1 g/24 h) on day 13. Renal function remained normal (creatinine clearance 105 ml/min (80-120 ml/min)). On day 18, with normal coagulation, a percutaneous renal biopsy was performed. Findings on light microscopy, immunofluorescence, and electron microscopic examination were consistent

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with minimal change glomerulopathy. The patient continued to receive prednisolone 30 mg a day, and treatment was started with cyclosporin A (CyA) 50 mg twice daily (2 mg/kg/day). The urinary protein excretion decreased to 0.2 g/24 h within two weeks. At six months' follow up the patient was well while receiving CyA 100 mg and prednisolone 7.5 mg daily, with no recurrence of synovitis or systemic disease. Renal function had remained normal (creatinine 82 µmol/l) and urine analysis negative.

Discussion

We have described the case of a 29 year old woman with AOSD who developed adult respiratory distress syndrome, nephrotic syndrome related to minimal change disease, and DIC after the start of intramuscular gold treatment.

AOSD is rare, with a reported prevalence of 1 per 100 000 adults aged between 16 and 35, and an equal male to female ratio.¹ First described by Bywaters in 1971, the disease has features similar to systemic onset juvenile idiopathic arthritis (JIA). There are now well established diagnostic criteria, which our patient fulfilled.¹

Patients with AOSD can, as in our case, develop multi-organ failure. This may be a manifestation of the disease itself.²⁻⁴ Alternatively, it may be a manifestation of MAS, which can complicate AOSD.⁵⁻⁶ MAS is caused by an excessive activation and proliferation of well differentiated macrophages, which actively phagocytose haematopoietic cells in the bone marrow of affected patients. Similar manifestations have been described in JIA after the start of gold treatment, typically after the second dose.⁷⁻⁸ Such a complication of gold has rarely been described in AOSD.⁹ Although our patient's deterioration may have been part of the natural history of AOSD, the coincidence with starting gold treatment makes a reaction to gold, as has been described in JIA, likely.

The nephrotic syndrome was a major component of our patient's illness. Nephrotic syndrome has been described in AOSD, though usually in the latter stages of disease secondary to renal amyloidosis.¹⁰ There has been one case report of a patient who developed AOSD and nephrotic syndrome simultaneously.¹¹ In this case a renal biopsy was not performed, but the nephrotic syndrome and AOSD went into remission with intravenous cyclophosphamide, raising the possibility that nephrotic syndrome is a complication of AOSD itself. In our patient the nephrotic syndrome developed after two doses of gold. Gold is certainly a well recognised cause of nephrotic syndrome secondary to membranous nephropathy, or less commonly minimal

change glomerulopathy.¹² However, the nephrotic syndrome usually develops after months or years of treatment and has not been previously described after two doses of gold.

Remission has been maintained in this patient with CyA. There is little published evidence for the use of CyA in AOSD. Marchesoni *et al* used low dose CyA in six patients with chronic or relapsing AOSD.¹³ Complete remission was seen in four patients and partial remission in two. Five were able to reduce or stop steroid treatment. There are only two other case reports of patients with AOSD being treated successfully with CyA.¹⁴⁻¹⁵ The observation that CyA can maintain remission in AOSD is interesting, and from a pathophysiological perspective highlights the potential role of T cells in the disease. The role for CyA in AOSD should be explored further.

Lessons

- Gold should be used with caution in AOSD
- Gold may acutely precipitate multi-organ failure and nephrotic syndrome in AOSD
- Cyclosporin A is a useful alternative to gold in the management of AOSD.

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