LETTERS

Alopecia areata and relapsing polychondritis or mosaic autoimmunity? The first experience of co-trimoxazole treatment

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A 13 year old girl presented with auricular chondritis and recurrent episodes of unexplained chest pain, arthritis, bronchitis, conjunctivitis, prolonged steroid resistant alopecia areata, and a history of recurrent tonsillitis. Both the mosaic of autoimmunity and relapsing polychondritis were considered in the differential diagnosis. The patient was successfully treated with co-trimoxazole. The significance of co-trimoxazole, which is an antibiotic and an immunomodulatory drug, in the treatment of autoimmune disease is discussed.

The term "mosaic of autoimmunity", introduced by Shoenfeld and Isenberg in 1989, implies clustering of several autoimmune diseases in a single patient. Relapsing polychondritis (RP) is a rare episodic inflammatory disease, which affects the cartilage of ears, respiratory tract, joints, and vessels and may be fatal. Drug treatment may control the disease activity in only some patients.[1] Alopecia areata (AA) affects anagen hair bulbs. T cell mediated and antibody dependent mechanisms have been suggested.[2 3] Glucocorticoids, anthralin, or minoxidil stimulate hair growth but do not prevent hair loss.[2] AA has been described in association with other autoimmune disorders. We believe this to be the first reported case in which AA is associated with auriculum chondritis and mosaic of autoimmunity which responded to co-trimoxazole treatment.

CASE REPORT

A 13 year old girl presented with acute inflammation of the left external ear. She had acute tonsillitis two weeks before the symptoms appeared, which was treated. Five years earlier the patient had recurrent attacks of chest pain, which resolved spontaneously. Four years earlier she began to have episodes of mono-oligoarthritis which resolved after 3–4 days. She had a long term history of recurrent tonsillitis. β-Haemolytic streptococcus was only once isolated on culture. Acute tonsillitis preceded episodes of arthritis on several occasions. Several events of acute bronchitis and recurrent conjunctivitis occurred during this period. Retinal examination was unremarkable.

Twenty months before the chondritis a large patch of AA appeared. Applications with betamethasone cream and 0.1–1% short contact anthralin treatment for three months failed to induce regrowth of hair. Oral prednisolone was started at an initial dose of 40 mg a day tapered over the next three weeks. The AA disappeared, but during the following months new adjacent patches appeared. Intermittent corticosteroid treatment with oral prednisone and intralesion scalp injections of betamethasone (Celestone) every 6–8 weeks[2] and local applications of 5% minoxidil spray for one and a half years promoted hair growth, yet additional patches of AA appeared.

The acute auricular inflammation, which spared the ear lobe, was diagnosed as chondritis. Intravenous amoxycillin-clavulanic acid was initiated, with no response noted after one week of treatment (fig 1A). An autoimmune aetiology of the disease was suspected. Oral prednisone 40 mg a day was instituted for five days and co-trimoxazole 50 mg/kg/day in two

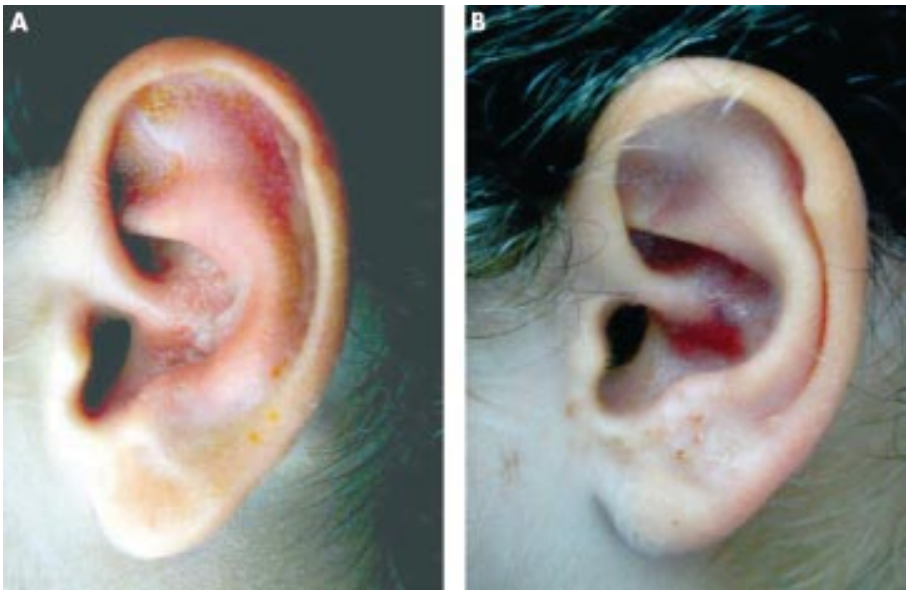

Figure 1 (A) Diffuse oedema and erythema of the auricle sparing the ear lobe are sustained after five days of intravenous augmentin (amoxycillin+clavulanic acid) treatment (1 g every eight hours). (B) Two days after the initiation of combined treatment with prednisone 40 mg/day and co-trimoxazole 50 mg/kg/day, there is marked diminution of the oedema and erythema.

divided doses was started as well. The rationale for co-trimoxazole treatment was its steroid sparing effect and antibiotic prophylaxis, which might prevent the possible adjuvant action of the pharyngeal flora on autoimmunity.[4] Prompt regression of the auricular inflammation was seen two days after starting the combined treatment (fig 1B), and within a few days complete resolution of the chondritis was noted. The daily co-trimoxazole treatment was reduced to 25 mg/kg after one week, taken as single dose. Two weeks later the therapeutic policy was 25 mg/kg every other day (taken as single daily dose), and this schedule was continued for five months. Two months after the initiation of the co-trimoxazole treatment the patches of AA disappeared.

Five months after the initial episode of chondritis a routine vaccination for tetanus and poliomyelitis was performed at school. Ten days later, the signs of chondritis recurred in the same ear. The co-trimoxazole dose was increased to the initial dose (50 mg/kg/day in two divided doses) without the addition of corticosteroids. After three days, complete recovery occurred and the alternate day dose schedule was restarted. An attempt to decrease the dose to 25 mg/kg/day twice a week for six weeks was performed but was associated with the appearance of two small foci of AA. Hair growth followed reinstitution of a daily regimen for one week followed by alternate day dose schedule (25 mg/kg/day every other day) for four weeks. During follow up, repeated tests for complete blood count, blood chemistry, antinuclear antibodies, anti-DNA, antinuclear cytoplasmic antibodies, IgG, IgA, IgM, complement, rheumatoid factor, protein electrophoresis, thyroid function were normal. Lung and heart imaging studies were unremarkable.

DISCUSSION

Mosaic of several autoimmune diseases or multiform RP should be considered when RP occurs in patients with other disease of autoimmune aetiology. No laboratory tests have been found to be diagnostic for these disorders. We propose that recurrent tonsillitis might be due to incompetent immune control of infection. IgA deficiency as a common denominator to the mosaic of autoimmunity and recurrent infections has not been detected. We treated our patient with co-trimoxazole, assuming that it might control bacterial load, on the one hand, and modulate the cellular and humoral immune response, on the other.[4] This modulation may have a role in the treatment of AA, which may be transferred by T lymphocytes.[5] In 1970, Ghilchik *et al* found that trimetoprim (component of co-trimoxazole) significantly extended the life of skin grafts transplanted from brown to white mice.[6] The prolongation of the rejection time was similar to that obtained with azathioprine. Inhibition of T lymphocytes by co-trimoxazole may be responsible for both late allograft rejection and therapeutic effect in AA. Co-trimoxazole was successfully used in the treatment of other autoimmune diseases.[4]

Alteration of the immune process by sulfasalazine (SSZ) through inhibition of nuclear factor-κB signalling activation, which contributes to anti-inflammatory and immunosuppressive effects, has been reported.[7] In another recent study patients with severe AA received SSZ and showed 23% of hair growth, which is cosmetically acceptable.[8] Sulfonamide sulfamethoxazole may have similar properties. It is known that patients with RP have increased titres of antibodies to cartilage proteins.[9] It is still unclear whether these antibodies are a result or cause of cartilage damage. These antibodies may have a role in cartilage inflammation and decrease after successful treatment. The presence of HLA-B8, DR3 has recently been found to be associated with multiple autoantibodies and autoimmunity.[10] Co-trimoxazole may cause a decrease in the IgM titre during treatment.[4] This may partially explain its efficacy in treating RP. After two months of co-trimoxazole treatment the steroid resistant AA was completely healed. No recurrence of tonsillitis or arthritis was noted during this period. Prompt resolution of relapsing chondritis and alopecia followed reinstitution of the appropriate co-trimoxazole dose. A decrease in lymphocytes blood count and serum IgG was noted during co-trimoxazole treatment (fig 2).

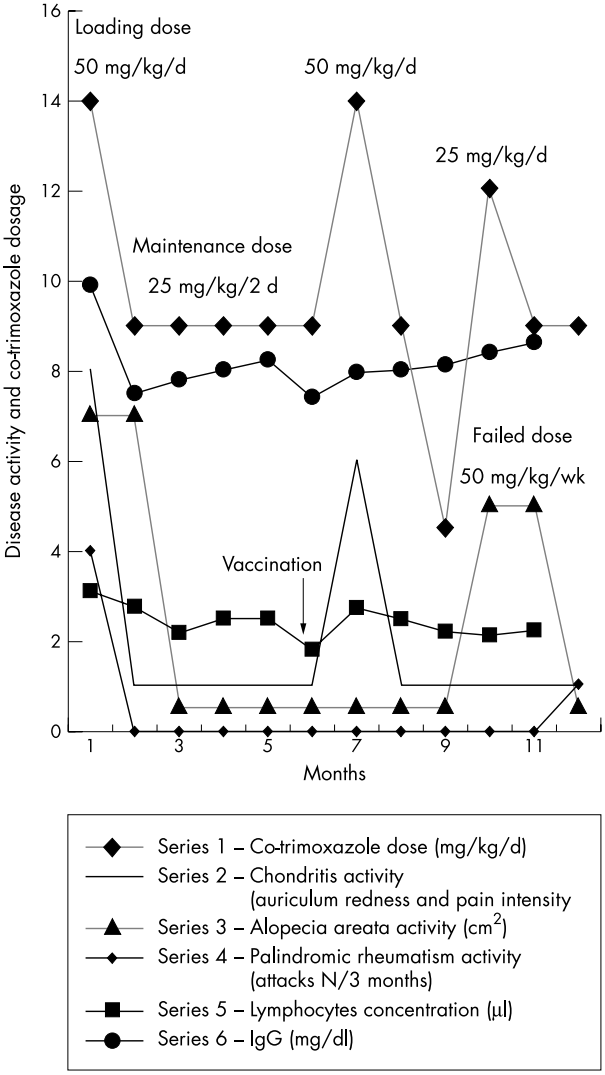

Figure 2 Monthly values of clinical features and laboratory findings.

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An unusual case of ANCA positive disease

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We report here on a patient in whom induction of myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA) occurred simultaneously with the development of pseudovasculitis due to the cholesterol emboli syndrome.

CASE REPORT

A 65 year old woman was admitted in August 2001 because of fatigue, weight loss, and oligoarthritis. She had a history of hypertension for which she was treated with captopril and hydrochlorothiazide. On examination she had acrocyanosis, livedo reticularis, a blood pressure of 220/110 on both arms, vascular bruits over the carotid and femoral arteries, and arthritis of the right wrist and both knees. The erythrocyte sedimentation rate (ESR) was 70 mm/1st h, C reactive protein (CRP) 75 mg/l, haemoglobin 7.1 mmol/l, and white blood cell count 10.8×10^9/l. Serum creatinine was normal and there were no abnormalities on urine analysis. Rheumatoid factor, antinuclear antibodies, ANCA, cryoglobulins, and anticardiolipin antibodies tested negative. Systemic vasculitis was suspected, but a deep muscle biopsy disclosed no abnormalities. Arteriography showed generalised atherosclerosis with bilateral stenosis of the renal arteries but no (micro-) aneurysms of the visceral arteries. Captopril was replaced by nifedipine and a bilateral stenting procedure of the renal arteries was performed, which improved the blood pressure. Because of persistent undifferentiated oligoarthritis, hydroxychloroquine was started.

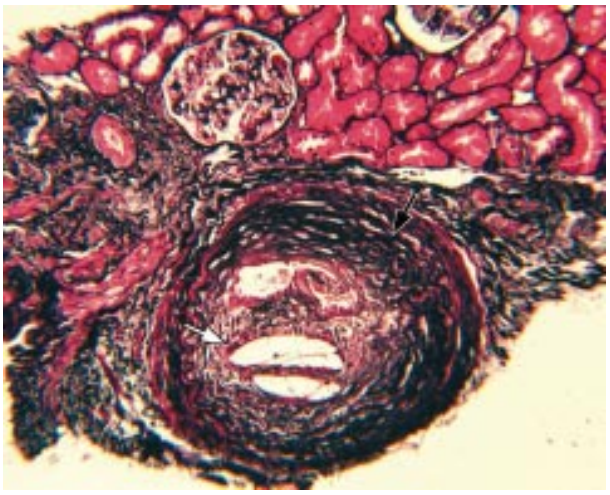

Figure 1 Kidney biopsy specimen showing cholesterol embolism (white arrow) in afferent arteriole with surrounding fibrosis (black arrow) (silvernitrate, ×320).

Two months later, the patient was readmitted because of fever, myalgia, and progressive renal failure. Shortly after admission she developed chest pain due to pleuropericarditis. The ESR was 132 mm/1st h, CRP 217 mg/l, haemoglobin 5.7 mmol/l, white blood cell count 19×10^9/l, and serum creatinine was 263 μmol/l. Proteinuria was 300 mg/l/24 h without erythrocyturia. Pleural fluid showed an exudate without malignant cells. All cultures remained sterile. On immunological testing a perinuclear ANCA was now detected and an enzyme linked immunosorbent assay (ELISA) showed that the MPO-ANCA was 39 arbitrary units (AU). Fundoscopy was normal and no vegetations were detected by echocardiography. Endoscopy of the nose, including biopsy samples, showed no abnormalities. A kidney biopsy showed multiple cholesterol emboli (fig 1). Because of persistent pleuritis, prednisolone 20 mg a day was started. At that time, renal function had already ameliorated spontaneously. During follow up in an outpatient department, the clinical condition of the patient improved further. At the last visit in March 2002, prednisolone was stopped. CRP had normalised and renal function stabilised at a serum creatinine around 140 μmol/l. The MPO-ANCA level was still positive at 22 AU in January and had become negative in March 2002.

DISCUSSION

Cholesterol emboli syndrome usually occurs in patients with severe atherosclerosis and is triggered in one third of patients by arteriography or an endovascular procedure.[1] Apart from the classical features, including acrocyanosis, livedo reticularis, and progressive renal failure, it may produce a variety of symptoms mimicking vasculitis.[2] Symptoms are caused by direct embolisation of the small and middle sized arteries. In addition, the presence of cholesterol emboli within the vascular lumen can trigger an inflammatory reaction.

Fever, weight loss, myalgia, leucocytosis, and raised ESR and CRP are well recognised manifestations of "pseudovasculitis" due to cholesterol emboli. Eosinophilia and hypocomplementaemia are often associated, though not in our patient. Pleuropericarditis has not yet been reported as a manifestation of pseudovasculitis due to cholesterol emboli. Isolated pleuritis was described in one case.[3] ANCA positivity has been reported occasionally.[1 2 4] In most of these cases ANCA was directed against MPO, as in our case. However, the induction of ANCA was not documented during the course of the cholesterol emboli syndrome in any of the patients.

Recently it has been shown that ANCA is not more prevalent in patients with atherosclerosis than in a human control group.[5] In vasculitis, a pathophysiological role for MPO-ANCA has been suggested by several authors.[6 7] It was demonstrated that the transfer of MPO to non-immunised mice results in the development of vasculitis.[7] Our patient initially had a mild vasculitis-like disease, probably due to cholesterol emboli, and