Letters to the Editor

Osteonecrosis of the knees in a variable common immunodeficiency

Sirs,

We report a case of osteonecrosis of the knees in a 37-year-old woman suffering from a common variable immunodeficiency since the age of 17. She presented at the age of 17 with spontaneous cutaneous ecchymosis revealing an autoimmune thrombopenic purpura treated by steroids during one year. At the same time a severe hypogammaglobulinemia of 3.5 g/l was discovered. Immunoglobulin G was assessed at 2.95 g/l (normal range: 6.39 - 13.5), IgA at 0.06 g/l (normal range:0.7 - 3.12) with normal IgM. By that time she was receiving polyvalent human intravenous immunoglobulins (IVIg) regularly every 3 weeks. During this period she presented repeated infections of the respiratory upper tract and sinuses.

In 1992 a moderate splenomegaly was discovered and in 1996 an autoimmune haemolytic anaemia responded to steroids in a few weeks. ln February 2000,she presented severe knee pain of sudden onset, increasing with cough. Her clinical examination was normal. The erythrocyte sedimentation rate (ESR) was 4 mm at one hour with normal fibrinogen and moderately increased C reactive protein at 18 mg/l. A full blood count found moderate pancytopenia related to hypersplenism. Antinuclear, anti-double-stranded DNA antibodies and antiphospholipids were normal. Knees radiographs were normal,as was a bone technetium scintigraphy. Because of the persistence of mechanical knee pain, however, a second bone scintigraphy was done and revealed abnormal uptake at the tibial plateaus. Magnetic resonance imaging of the femoral condyles showed metaphysis and diaphysis lesions of the femurs and tibias with a central high signal on T1-weighted images, a polycyclic surround of low signal on T1-weighted images, and a double halo on T2-weighted images. These MRI aspects were consistent with multiple osteonecrosis of the knees.

Common variable immunodeficiency (CVI) is a primary immunodeficiency disease characterized by hypogammaglobulinemia and reccurent bacterial infections (1). The clinical spectrum of CV1 and immunological features are heterogenous. Sometimes CVI is associated for unknown reasons with autoimmune [such as systemic lupus erythematosus (SLE)] or granulomatous diseases (1). Moreover, patients with CVI present an increased risk of neoplasms, particularly lymphoma (1).

Osteonecrosis of the knee is relatively frequent,with two distinct forms:the idiopathic form in which no factors for osteonecrosis can be found, and a secondary form in which predisposing factors can be recognised (2). Aetiological factors in secondary knee osteonecrosis are alcoholism, SLE, administration of systemic steroids, Gaucher's disease, drepanocytosis and thalassemia. Secondary osteonecrosis, such as our case, is more frequent in younger patients, with larger lesions than idiopathic osteonecrosis,affecting both knees in 30-80% of cases but usually with a gradual onset (2). We report here the first case of osteonecrosis described in a patient with a common variable immunodeficiency. ln our case, the possibility of a steroid-induced osteonecrosis could also be considered because the patient frequently received systemic steroids during repeated respiratory upper tract infections and for autoimmune thrombopenia and haemolytic anaemia. Although no cases of osteonecrosis after IVIg have been described, a possible role of hyperviscosity can also be hypothesised as one of the factors contributing to bone medullary ischemia (3). Indeed, retinal vein occlusions following IVIg have been reported (4). Osteonecrosis has also been described in human immunodeficiency viral infection; the mechanism is unknown, but could merely involve an increased frequency of risk factors (5-7). This could support the hypothesis of a relationship between common variable immunodeficiency and osteonecrosis in our case, notwithstanding the fact that a fortuitous association cannot be excluded.

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Detection of anticardiolipin antibodies

Sirs,

The editorial by Drs. Tincani and Meroni gives a rather misleading interpretation of an article that we published in the same issue (1,2). We demonstrated in our study that, whereas using a virtually identical approach other colleagues in our laboratory had been able to detect anti-DNA antibodies in patients with lupus, we had been unable in spite of a dozen different variations in the basic cell culture and antibody visualisation techniques to detect anticardiolipin antibodies in culture supernatants of peripheral blood mononuclear cells from patients with the antiphopsholipid antibody syndrome.

We concluded that other methods of measuring anticardiolipin antibodies produced in culture will need to be explored but not (as Tincani and Meroni implied) that there were no antibodies produced to be measured. We had certainly speculated that this problem might arise through antibody-producing cells being absent from the peripheral blood but concluded that this hypothesis was unlikely. We further concluded that there may have been a methodological problem inherent in our techniques which we had been unable to overcome within the time available and suggested that there was little to be gained from further perseverance. We believe, in fact, it is more likely that the phospholipids present in the culture supernatants, as a result of cell death, are neutralising any antiphospholipid antibodies produced, and thus rendering them undetectable. We would anticipate that similar problems might arise when looking for anti-beta 2GP1 antibodies. Ours was, therefore, intended to be a friendly note of caution to those interested in the field that potentially significant problems exist in trying to identify anticardiolipin antibodies in the supernatant of PBMC compared to the detection of DNA antibodies. We naturally wish any other group who attempt to go

down this road the very best of luck!

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Combining cyclosporine with prevailing antirheumatic drug therapy in the treatment of juvenile idiopathic arthritis

Sirs,

The effect of cyclosporine either alone or in combination with various disease modifying antirheumatic drugs (DMARD), mainly methotrexate, has been shown in rheumatoid arthritis (1). However, there is little data on the effect of cyclosporin in the treatment of juvenile idiopathic arthritis (JIA) and they have mainly focused on the systemic onset type of the disease (2). There are no studies which have assessed the effect of a combination of cyclosporine with other DMARDs in JIA. We retrospectively analysed the usefulness of adding cyclosporine to the treatment protocol in 32 children (27 girls and 5 boys) with active JIA resistant to conventional DMARD therapy, which in all cases included methotrexate. The mean (SD) age of the patients was 9.1 (± 2.8) years. The onset type of the disease was: extended oligoarthritis (n=6), oligoarthritis (n=4), polyarthritis (n=19) and systemic onset JIA (n=3). Fourteen patients had iritis at the onset of cyclosporine treatment.

After the onset of cyclosporine treatment most patients continued to use their earlier DMARD combination including methotrexate in every case. Cyclosporine plus methotrexate was combined with two other DMARDs in 6 patients, with one DMARD in 16 patients, and 10 patients had a simple cyclosporine plus methotrexate combination. The drugs in the combinations were methotrexate (n=32), natrium aureothiomalate (n=2), sulfasalazine (n=8), hydroxychloroquine (n=17), and azathioprine (n=1). The prevailing drug therapy remained stable, and we did not include in this analysis patients in whom the DMARD therapy had been changed. At the onset of cyclosporine treatment, the mean starting dose of methotrexate was 20.1 mg/week in the 14 patients who used it *per os* and 21.4 mg in the 18 patients who received it parenterally. The mean initiating dose of cyclosporine was 2.5-3 mg/kg/day. Sixteen (50%) out of the 32 patients took cyclosporine for at least two years. Side effects were monitored following good clinical practice with special attention devoted to blood pressure and renal function, measured by the level of serum urea, and by the creatinine clearance test in cases with a suspicion of impaired renal function.

For this study the effect of treatment and the side effects were checked from the medical records up to 2 years from the onset of the treatment. The treatment effect was assessed as a change in hospitalisation days and in prednisolone dose, and by the common inflammatory indexes, i.e. the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Our treatment policy includes treating all clinically active joints with intra-articular corticosteroids. Thus, for this retrospective study we also considered the change in the number of active joints as an outcome measure of disease activity. The data were assessed by intention-to-treat (ITT) analysis after to years from the onset of cyclosporine treatment. The last observation carried forward (LOCF) was used when there were missing clinical and laboratory data.

Table I shows our main results. Both ESR and CRP showed a significant reduction, while there was a significant increase in the need for hospitalisation and for intra-articular corticosteroid injections. One patient with polyarthritis had a remission after 6 months which lasted up to the two-year check-up. Side effects were frequent but usually mild or reversible, and did not require in any case the cessation of the therapy. In 2 cases with iritis the signs of inflammation totally disappeared; in one of them, however, the follow-up had lasted only one year. In addition,6 patients initially showed improvement in their iritis, but this was restricted to the first 6-month period.

In conclusion,this series represented active, severe cases of JIA who were aggressively treated with various DMARD combinations without achieving disease control. In all cases we added cyclosporine to the prevailing drug therapy which included methotrexate. After adding cyclosporine to the prevailing DMARD combination there was a significant reduction in laboratory indexes of inflammation. On the other hand, there was an increase in the number of intra-articular corticosteroid injections needed and in the number of hospitalisation days. Moreover, spontaneous fluctuations in different factors that represent disease activity can modify the result. Overall our results are based on retrospective data and must be considered preliminary. Though all of the patients had methotrexate and cyclosporine as a minimum combination, 2/3 of the patients in the series had additional DMARDs which invalidizes the analysis as to a given drug combination. Mild side effects were frequent, but adverse effects were not seen. We are awaiting controlled studies on this important topic.

Table I. Outcome in 32 JIA patients after adding cyclosporine to the prevaling DMARD treatment.

Variable	Baseline Median (IQR)	At 24 months Median (IQR)	Median change[3] Median (95% CI)	p-value[4]
Hospitalisation days[1]	5.5 (4.0, 7.5)	9 (4, 15)	4 (0.5 to 7.0)	0.040
Prdn, dose, mg[2]	10.0 (7.5, 15.0)	10 (7.5, 17.0)	0 (-2.5 to 2.5)	0.82
GC injections[1], n	3 (1.5, 5.0)	4.5 (2, 8)	2 (0.5 to 4.0)	0.022
ESR, mm/h	36 (18, 52)	20 (12, 36)	-10 (-1.5 to -22.0)	0.012
CRP, mg/l	27 (5, 71)	2 (0, 12)	-28 (-8.0 to -40.5)	< 0.001
fS-urea mg/l	3.8 (3.2, 4.6)	4.2 (3.6, 5.5)	0.5 (-1.0 to 1.2)	0.088

[1]Calculated within 3-month periods; [2]Every other day; [3]Rank-based confidence interval for difference in paired medians; [4]Kornbrot's rank difference test. IQR = interquartile range.

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