

LETTERS TO THE EDITOR

Sporotrichial Bursitis

SIR—Sporotrichosis involving osteoarticular structures like joints, bursae or bones is an extremely rare disease. Herein, we describe the third case of sporotrichial bursitis reported in the English language medical literature.

A 50-yr-old Caucasian woman was referred because of pain and swelling of the right knee. She was a healthy homemaker whose hobby was gardening. She had no known debilitating condition, nor was she under glucocorticoid treatment. Her disease had started 12 days earlier with the abrupt onset of pain, swelling and erythema on the anterior aspect of her right knee without obvious trauma, prick or wound in the area. Three days later, low-grade fever of 37.8°C started without chills. On examination, tenderness and erythema of the prepatellar bursa with fluctuation were evidenced without involvement of the knee. The prepatellar bursa was drained by closed needle puncture which yielded a few drops of synovial fluid. Gram staining and examination with polarized light microscopy were both unrevealing. Cultures of synovial fluid and blood samples were negative after 7 days of incubation in the usual media for aerobic and anaerobic microorganisms, a method not suitable for the isolation of *Sporothrix*. Radiography of the knees showed soft-tissue swelling. The differential blood cell count was within normal limits and the ESR was 46 mm. Empirical treatment with i.v. cloxacillin and repeated needle drainage was started without success. A surgical bursectomy was indicated on day 5 of hospitalization. Pathological examination of the tissue revealed a mixed purulent exudate and an epithelioid cell granulomatous reaction with giant cells. The infiltrate contained fungi with 'cigar', round yeast and variously shaped budding forms (Fig. 1). The fungus cells stained with PAS, methenamine silver and Giemsa stain. Tissue samples were not cultured. Despite the patient rejecting antifungal treatment, surgical removal of the bursa resulted in the complete resolution of the process.

The involvement of the musculoskeletal system in sporotrichosis is rare [1, 2]. It includes arthritis, bursitis, granulomatous tenosynovitis, osteitis and granulomatous myositis. Frequently patients are misdiagnosed as having rheumatoid arthritis [3, 4], tuberculous arthritis [5], gout [6], or non-specific tenosynovitis [7]. The disease follows an indolent course and the diagnosis is usually delayed. The pattern of joint involvement can be mono-, oligo- or polyarticular mimicking rheumatoid arthritis [3–5]. Synovial fluid may be serosanguineous and inflammatory with low glucose levels. The diagnosis is based on the culture of the micro-organism in a tissue specimen or synovial fluid. We did not obtain a positive culture, but the pathologic

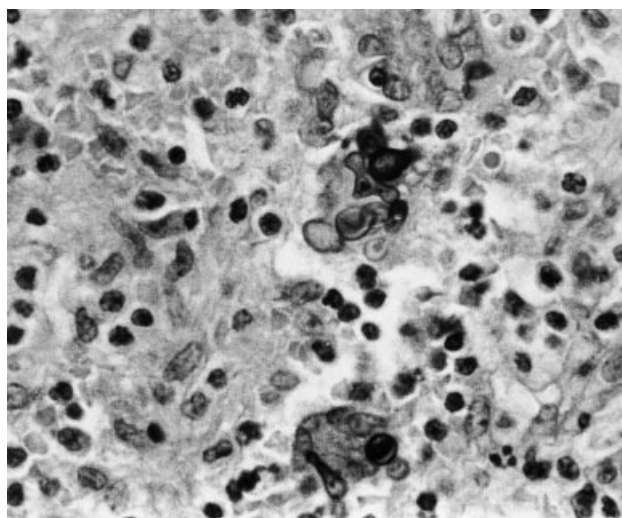


FIG. 1.—Mixed inflammatory infiltrate with budding yeast [PAS × 300].

picture showed epithelioid cell granulomatous reaction containing the typical 'cigar' and round yeast forms of *Sporothrix* sp. As these findings cannot be attributed to any other process, we made the diagnosis of sporotrichial bursitis despite the absence of confirmatory cultures. To the best of our knowledge, the present case is the third case of sporotrichial bursitis reported in the English language medical literature. Levinsky reported a case of olecranon bursitis in a 68-yr-old man that was initially misdiagnosed as gout [6]. Manhart *et al.* [8] reported the case of a 61-yr-old man with bone marrow hypoplasia and under chronic glucocorticoid treatment who developed olecranon bursitis [8]. In both cases, treatment with potassium iodide and amphotericin B resolved the disease, although Manhart's patient required bursectomy. Selected cases, with no known immunosuppression or debilitating disease and with well-circumscribed disease, can be cured by simple excision of the infected tissue, as our case exemplifies.

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1. Lurie HI. Five unusual cases of sporotrichosis from South Africa showing lesions in muscles, bones and viscera. *Br J Surg* 1963;50:585–91.

2. Riggs S, Moore AJ, Gyorkey F. Articular sporotrichosis. *Arch Intern Med* 1966;584-7.
3. Ricca LR. Articular sporotrichosis: Report of a case simulating rheumatoid arthritis. *J Florida Assoc* 1969;56:329-30.
4. Molstad B, Strom R. Multiarticular sporotrichosis. *J Am Med Assoc* 1978;240:556-7.
5. Bayer AS, Scott VJ, Guze LB. Fungal Arthritis III. Sporotrichal arthritis. *Semin Arthritis Rheum* 1979;9:66-74.
6. Levinsky WJ. Sporotrichial arthritis: report of a case mimicking gout. *Arch Intern Med* 1972;129:118-9.
7. Schwartz DA. Sporothrix tenosynovitis—differential diagnosis of granulomatous inflammatory disease of the joints. *J Rheumatol* 1989;16:550-3.
8. Manhart JW, Wilson JA, Korbitz BC. Articular and cutaneous sporotrichosis. *J Am Med Assoc* 1970;214:365.

Non-Hodgkin's Lymphoma of the Femur Presenting as a Pathological Fracture in a Patient with Lupus/Sjögren's Syndrome Overlap

SIR—Sjögren's syndrome (SS) is a multisystem autoimmune disease, which can evolve to B-cell lymphoid malignancy, usually indolent centrocytic or monocytoid nodal or gut associated, but isolated high-grade extranodal lymphoma arising *de novo* has rarely been described [1, 2].

A 68-yr-old female presented in May 1990 with a history of tiredness, a distal purpuric rash, polyarthralgia, mild peripheral paraesthesiae and aching over the right parotid gland. Symptoms of sicca, photosensitivity and Raynaud's phenomenon were absent.

Examination showed mild synovitis in the small joints with no rheumatoid deformities or nodules, but a fading purpuric-vasculitic rash on her legs.

Investigations showed Hb 113 g/l, a low white cell count ranging from 3.1 to $4.5 \times 10^9/l$ with lymphopenia $0.2-0.4 \times 10^9/l$. The erythrocyte sedimentation rate (ESR) ranged from 40 to 60 mm/h, serum immunoglobulin levels were normal except for IgM at 3.9 g/l (normal 0.50-2.00). Protein electrophoresis showed no paraprotein. Serology showed negative rheumatoid factor, but positive antinuclear factor (homogeneous pattern; titre 1:160). She was negative for DNA binding antibodies, positive for anti-Ro antibody, but negative for anti-La. Radiography of her hands and feet showed no erosions. Neurophysiological tests confirmed a mild peripheral neuropathy. Lip biopsy showed lymphocytic infiltration consistent with SS. Therefore, a diagnosis of SS with lupus overlap was made, despite the absence of any clear sicca syndrome [3-5].

In October 1992, following a slight slip on the stairs, her left knee became progressively more swollen and painful, with a flexion deformity.

Radiograph of the left knee (Fig. 1) showed an unsuspected supracondylar fracture in an area of abnormal bone with periosteal reaction suggestive of metastatic tumour. Open biopsy revealed a high-grade non-Hodgkin's B-cell lymphoma (Fig. 2) with tumour cells positive for leucocyte common antigen (Dako) and negative for CAM 5.2 (epithelial marker) (Becton Dickinson). The cells were positive for the B-cell marker CD20 (L26) (Dako) and only very occasional

cells were positive for the T-cell marker CD3 (Dako). Further tests failed to show any organ involvement or diffuse lymphoma. The patient was treated with local radiotherapy followed by CHOP (cyclophosphamide, doxorubicin, vincristine and high-dose oral methylprednisolone). The fracture healed slowly and her subsequent progress has been satisfactory.

A diagnosis of SS with lupus overlap in this patient, rather than SLE or another CTD, was based on the clinical and laboratory findings described above [3-6]. Bone neoplasms may well present with a pathological fracture of the type exhibited by our patient. We are,



FIG. 1.—Radiograph showing a pathological supracondylar fracture of the left femur.

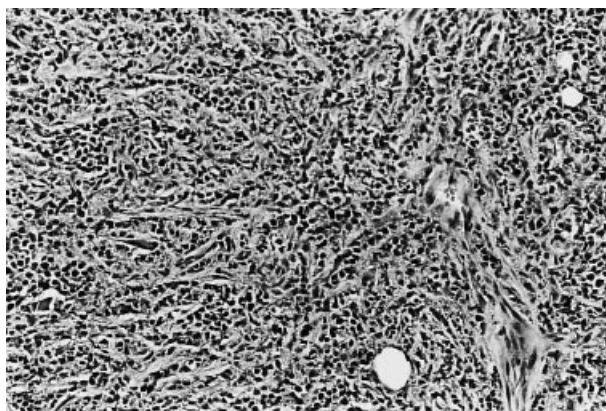


FIG. 2.—Section showing diffuse infiltration by lymphoma cells (H & E stain).

however, unaware of any previous report of non-Hodgkin's lymphoma of the bone presenting in a similar manner in a patient with SS or indeed other CTDs. It is unlikely that this patient had a grumbling lymphoma when first seen because she had no complaints whatsoever in the affected area and the high-grade non-Hodgkin's lymphoma subsequently shown is unlikely to present in a protracted manner over 3 yr.

Lymphoma occurs more frequently in primary SS patients than in the general population [1, 2, 4]. A 44-fold increased risk had been suggested [2], but this report from a tertiary centre was highly selective and may have overestimated the risk. Our own experience suggests that this may be so, as we found a relative risk of only 14 in our Sjögren's population [4, 5].

The extranodal lymphomas usually affect the salivary glands or gastrointestinal tract and are chiefly B-cell neoplasms, although monocytoid differentiation has been described. Early diagnosis and appropriate aggressive management are vital as the neoplastic process can be controlled adequately if treatment is instituted early. This is well demonstrated by our patient's excellent progress over 5 yr since diagnosis of the lymphoma with no signs of recurrence to date.

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1. McCurley TL, Collins RD, Ball E. Nodal and extranodal lymphoproliferative disorders in Sjögren's syndrome: a clinical and immunopathologic study. *Hum Pathol* 1990;1:482-92.
2. Kassan S, Thomas T, Moutsopoulos HM *et al*. Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978;89:888-92.
3. Daniels TE, Talal N. Diagnosis and differential diagnosis of Sjögren's syndrome. In: Talal N, Moutsopoulos HM, Kassan SS, eds. *Sjögren's syndrome: clinical and immunological aspects*. Berlin: Springer-Verlag, 1987:193-9.
4. Pal B. A clinical and laboratory study of 219 patients with Sjögren's Syndrome in North-East England. MD Thesis, University of Newcastle Upon Tyne, 1988.
5. Kelly CA, Foster H, Pal B, Gardiner P, Malcolm AJ, Charles P *et al*. Primary Sjögren's syndrome in North East England—a longitudinal study. *Br J Rheumatol* 1991;30:437-42.
6. Pal B, Griffiths ID. Primary Sjögren's Syndrome presenting as osteomalacia secondary to renal tubular acidosis. *Br J Clin Pract* 1988;42:436-8.

Management of Dermato-Rheumatic Syndromes

SIR—We read with interest the editorial in *British Journal of Rheumatology*, Vol. 36, No. 4, 1997, written by C. E. Griffiths. We substantially agree with his opinion that the treatment of psoriatic arthritis (PA) by rheumatologists without them consulting their dermatologist colleagues may result in dermatological difficulties.

To prevent such problems, Professor Griffiths recommends a close collaboration with multidisciplinary clinics, including both dermatologists and rheumatologists, for managing patients suffering from severe psori-

asis with concomitant arthritis. In the following, we would like to present our own experiences in this field.

Considering the fact that dermatology and rheumatology have numerous points of contact in common, and that patients often need the help of both specialties, an interdisciplinary consultation panel was set up as early as 1978 at the Jena University Hospital (Germany) involving dermatologists and rheumatologists initially and specialists in physiotherapy and rehabilitation later. So far, some 1800 patients with severe dermatological and rheumatological disorders, but with predominantly uncertain diagnoses, have been examined, advised and treated. The patients came from the dermatological and rheumatological units or were referred by specialists outside the hospital.

Of these patients, 28% suffered from PA, 15.1% from systemic lupus erythematosus (SLE), 6.1% from vasculitis syndromes, 8.1% from scleroderma, especially from progressive systemic forms, 2.5% from dermatomyositis and 7% from cutaneous forms of lupus. In 10% of cases, the diagnoses remained uncertain at the first visit. In 23.2%, patients presented with both rheumatological and dermatological symptoms/diseases independently (e.g. fibromyalgia and psoriasis or rheumatoid arthritis and seborrhoeic eczema, respectively).

In addition to the great advantage of exact and prompt diagnosis offered by interdisciplinary teamwork, the therapeutic implications were far-reaching. In 13% of patients, necessary topical or systemic pharmacotherapy was initiated for the first time. In 8% of patients, we were able to stop previous therapy without substitution. In 28% of cases, we realized a fundamental change in pharmacotherapy (e.g. starting with an immunosuppressive therapy after NSAID or corticosteroids). In 34% of patients, we saw a moderate modification of pharmacotherapy (i.e. change of DMARD, additional prescribing of NSAID or low-dose steroids, dose variation, change of topical pharmacotherapy). Finally, we introduced or changed physiotherapy in 65% of cases.

We are convinced that such teamwork has great advantages for both patients and medical specialists. Ultimately, the diagnostic procedure will be prompter and less expensive. This is also true for the therapeutic procedure. Moreover, possible adverse effects of rheumatological pharmacotherapy on the skin of patients with combined dermatological/rheumatological syndromes (e.g. PA, SLE) may be reduced or even prevented.

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1. Wollina U, Barta U, Tanner E, Uhlemann C, Hein G, Knopf B. Interdisziplinäre Betreuung von Patienten mit Kollagenosen—das Jenaer Modell. *Z Hautkrankh* 1993;68:602-6.

No Additive Effect of Cyclosporin A Compared with Glucocorticoid Treatment Alone in Giant Cell Arteritis: Results of an Open, Controlled, Randomized Study

SIR—Giant cell arteritis (GCA) is an inflammatory T-cell-dependent disease of large and medium-sized arteries, occurring in patients aged over 50 yr. Patients requiring prolonged treatment with glucocorticoids of >7.5 mg of prednisone/day have an increased risk of developing adverse effects [1]. Consequently, an alternative treatment to systemic glucocorticoids is desirable. Cyclosporin A (CsA) might be such a drug with selective immunosuppressive properties on the T-cell population [2]. We report the results of a 6 month,

open, randomized study, including two out-patient wards of the Sahlgrenska University Hospital with 20 and two patients from the rheumatology and the infectious disease departments, respectively. A central list of randomization was used and assessment criteria included laboratory parameters, tolerability and efficacy on low-dose CsA in combination with glucocorticoids in GCA.

All patients were included if they had confirmed GCA, according to the criteria of Bengtsson and Malmvall [3], and had had GCA for at least 1 yr and still needed >5 mg prednisone to suppress the inflammatory activity. The mean duration of GCA before entering the study was 39 months (range 12–72). The patients were randomly allocated to either CsA treatment in combination with prednisone or continued traditional treatment with glucocorticoids alone for a period of 6 months. Further details on the demographic data are given in Table I.

A low-dose CsA regimen was used with a starting dose of CsA of 2.0 mg/kg/day. The steroid dose was reduced according to each patient's clinical condition. The patients were evaluated at baseline and then after 1, 2, 4 and 6 months. The two groups were balanced in terms of prednisolone treatment and disease activity at baseline (Table II).

A total of 21 out of 22 patients completed the 6 month trial. Our results show a statistically significant decrease in the prednisone dose after 6 months in both the CsA–prednisone group and the group treated with prednisone only. There was no significant difference between the two groups. No severe adverse effects of low-dose CsA were noted. Two patients required a temporary or permanent decrease of CsA because of poor tolerance, and four patients because of high levels of CsA in the blood [4]. One patient was withdrawn because of temporary side-effects with liver dysfunction and neurological disturbances.

The main reasons to start therapy with glucocortic-

TABLE I
Clinical characteristics of 22 patients with giant cell arteritis at baseline

	Prednisone Mean ± S.D.	Prednisone and cyclosporin A	
		Mean ± S.D.	P
No. of patients	11	11	ns
Female/male	11/0	9/2	ns
Mean age, yr (range)	75.7 (60–88)	70.5 (59–77)	ns
Duration of previous treatment, months	42 ± 25	37 ± 25	ns
Height (cm)	163 ± 12	165 ± 6	ns
Weight (kg)	65.1 ± 18	77.5 ± 12	ns
BMI (g/cm ²)	24.0 ± 4.9	28.8 ± 4.4	ns
Clinical subgroups			
TA	7	5	
PMR	3	4	
TA and PMR	1	2	
Concomitant diseases			
Diabetes mellitus	1	2	
Hypertension	2	1	
Coronary artery disease	1	2	
Fracture of vertebrae	2	1	

TA, temporal arteritis; PMR, polymyalgia rheumatica; TA and PMR, combination of TA and PMR; BMI, body mass index.

TABLE II
Clinical outcome in 22 patients with giant cell arteritis treated with the combination cyclosporin A and prednisone or prednisone alone

		Prednisone and cyclosporin A			Prednisone		
		Mean ± S.D.			Mean ± S.D.		
		Entry	24 weeks	P	Entry	24 weeks	P
Laboratory	Erythrocyte sedimentation rate (mm/h)	36 ± 19	38 ± 22	ns	27 ± 29	25 ± 25	ns
	No. of patients with ESR > 30 mm/h	5	7		4	2	
	C-reactive protein (mg/l)	10 ± 12	27 ± 23	ns	26 ± 25	16 ± 15	ns
	No of patients with CRP > 15 mg/l	0	3		2	1	
Clinical parameters	Creatinine (mmol/l)	98 ± 12	96 ± 15	ns	91 ± 16	98 ± 15	0.03
	Systolic blood pressure (mmHg)	150 ± 14	150 ± 12	ns	153 ± 16	150 ± 13	ns
	Diastolic blood pressure (mmHg)	83 ± 12	87 ± 6	ns	84 ± 5	86 ± 2	ns
	Morning stiffness (min)	46 ± 73	6 ± 18	ns	67 ± 93	37 ± 74	ns
	Patient's assessment of disease activity, scale 1–5 (range)	2.3 (2–4)	1.3 (1–3)	0.03	2.2 (2–5)	1.7 (1–5)	ns
	Doctor's assessment of disease activity, scale 1–5 (range)	1.9 (2–4)	1.3 (2–3)	0.01	2.1 (2–5)	1.9 (2–5)	ns
	Treatment	Cyclosporin A dosage (mg/kg/day)	1.9 ± 0.7	1.7 ± 0.7	ns		
	Prednisone dosage (mg/day)	11.8 ± 10	6.4 ± 4	0.01	11.1 ± 7	7.6 ± 5	0.03
	Accumulated prednisone dose taken during study period (g)		1.41			1.44	

oids and a second immunosuppressive agent are steroid-resistant disease or the need for steroid-sparing measures due to side-effects. The studies in which a second drug has been added to steroid treatment are few and often based on small numbers of patients. In two prospective studies, the steroid-sparing effect of combined therapy was demonstrated for azathioprine [5] and methotrexate [6]. Patients requiring prolonged treatment with glucocorticoids in dosages >15 mg daily constitute a minority of all GCA patients and are considered to have steroid-resistant disease [7]. The positive effect of additive immunosuppressive treatment may be greater in this group and indeed three of the patients in the present study, on high steroid doses for a long time, were able to reduce their steroid dose to half or less compared to the start point. These patients are rare, however, and a multicentre study is therefore needed for further evaluation of combined therapy with CsA.

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1. Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis II. Relation between steroid dose and steroid associated side effects. *Ann Rheum Dis* 1989;48:662–6.
2. Murphy NG, Zurier RB. Treatment of rheumatoid arthritis. *Curr Opin Rheumatol* 1991;3:441–8.
3. Bengtsson BÅ, Malmvall BE. The epidemiology of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. *Arthritis Rheum* 1981;24:899–904.
4. Holt DW, Johnston A, Roberts NB, Tredger JM, Trull AK. Methodological and clinical aspects of cyclosporin monitoring: report of the Association of Clinical Biochemists task force. *Ann Clin Biochem* 1994;31:420–46.
5. De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. *Ann Rheum Dis* 1986;45:136–8.
6. Ferraccioli GF, Salaffi F, de Vita S, Casatta L, Bartoli E. Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. *J Rheumatol* 1996;23:624–8.
7. Wilke SW, Hoffman GS. Treatment of corticosteroid-resistant giant cell arteritis. *Rheum Dis Clin North Am* 1995;21:59–71.

Mannose-binding Protein Gene Polymorphism in South African Systemic Lupus Erythematosus

SIR—Mannose-binding protein (MBP) is a serum acute-phase protein which is able to activate the classical and alternative pathways of complement independent of antibody [1]. Dysfunctional alleles of MBP are present at a high frequency in healthy populations [2].

It has been reported that dysfunctional MBP alleles may be weak genetic susceptibility factors for systemic lupus erythematosus (SLE) in UK [3], Chinese [4] and Spanish [5] populations. These dysfunctional MBP alleles may predispose to SLE by acting as partial complement deficiency states, which are associated

with SLE in a variety of populations [6, 7]. We have now examined the frequencies of dysfunctional MBP alleles in Black South African SLE patient and control populations.

Fifty Black SLE patients from the Sotho and Zulu tribes, and 87 geographically and ethnically matched healthy control subjects, were studied. All SLE patients fulfilled the 1982 revised ACR criteria for SLE. MBP typing for polymorphism at codon 54 [8] and codon 57 [2] of exon 1 was accomplished using ARMS-PCR techniques, as previously described [3, 5]. Differences in the frequency of dysfunctional MBP alleles between SLE patients and controls were expressed as odds ratios (OR) with 95% confidence intervals (95% CI).

Dysfunctional MBP alleles caused by a mutation in codon 57 of the MBP gene were present in 54% of SLE patients and 45% of controls (OR = 1.4, 95% CI = 0.7–2.9). Dysfunctional alleles caused by a mutation in codon 54 were present in 15% of SLE patients and 11% of controls (OR = 1.4, 95% CI = 0.5–4.0). Sixty per cent of SLE patients possessed at least one dysfunctional MBP allele, compared to 46% of controls (OR = 1.7, 95% CI = 0.8–3.6).

Thus, a non-significant increase in the frequency of dysfunctional MBP alleles was observed in South African SLE patients vs controls. It is possible that the high frequency of dysfunctional MBP alleles among the South African control population may account for the lower strength of association seen compared to those in other populations [3–5]. This high frequency among healthy individuals may reflect a biological advantage conferred by dysfunctional MBP alleles [2, 9], which is of greater importance in South Africa than in Europe or Hong Kong. Alternatively, this difference in frequency may be due to genetic drift.

The results of our study suggest that there may be an increase in dysfunctional MBP alleles in the South African SLE population as in other ethnic groups. However, the effect, if it is real, seems to be weak and will need confirmation in larger studies. Approximately three times the number of cases and controls would be required to confirm significance at the 5% level with 80% power.

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1. Turner MW. Mannose-binding lectin: the pluripotent molecule of the innate immune system. *Immunol Today* 1996;17:532–40.
2. Lipscombe RJ, Sumiya M, Hill AVS *et al*. High frequencies in African and non-African populations of independent mutations in the mannose binding protein gene. *Hum Mol Genet* 1992;1:709–15.
3. Davies EJ, Snowden N, Hillarby MC *et al*. Mannose-binding

- protein gene polymorphism in systemic lupus erythematosus. *Arthritis Rheum* 1995;38:110–4.
4. Lau YL, Lau CS, Chan SY, Karlberg J, Turner MW. Mannose-binding protein in Chinese patients with systemic lupus erythematosus. *Arthritis Rheum* 1996;39:706–8.
 5. Davies EJ, Teh L-S, Ordi-Ros J *et al.* A dysfunctional allele of the mannose binding protein gene associates with systemic lupus erythematosus in a Spanish population. *J Rheumatol* 1997;24:485–8.
 6. Arnett FC, Reveille JD. Genetics of systemic lupus erythematosus. *Rheum Dis Clin North Am* 1992;18:865–92.
 7. Moulds JM, Krych M, Holers VM, Liszewski MK, Atkinson JP. Genetics of the complement system and rheumatic diseases. *Rheum Dis Clin North Am* 1992;18:893–914.
 8. Sumiya M, Super M, Tabona P *et al.* Molecular basis of opsonic defect in immunodeficient children. *Lancet* 1991;337:1569–70.
 9. Garred P, Harboe M, Oettinger T, Koch C, Svejgaard A. Dual role of mannan-binding protein in infections: another case of heterosis? *Eur J Immunogenet* 1994;21:125–31.

Diffuse Proliferative Glomerulonephritis in Behçet's Syndrome

SIR—Behçet's syndrome (BS) is a systemic vasculitis principally involving veins, venules and capillaries from multiple organs, with widespread manifestations [1]. However, renal involvement has been reported only occasionally. We describe a patient with active BS who developed an exudative mesangiocapillary glomerulonephritis with C3 and IgM deposition.

A 70-yr-old male was admitted in April 1995 with a history of severe hypertension and malleolar oedema for 1.5 months. There had also been recurrent oral ulcers for the last 19 yr. Fifteen years ago, he developed a monocular right-sided uveitis, a distal superficial venous thrombophlebitis of the right leg, and a cutaneous vasculitis, and the diagnosis of BS was made. There was no history of genital ulcers, erythema nodosum or arthritis. In the last 5 yr, he developed a mild hypertension, which was well controlled with a low-sodium diet and minimal doses of hydrochlorothiazide. Renal function and urinalysis were normal. Three months prior to the admission, the patient referred with parieto-occipital oppressive headache and a severe increase in blood pressure was observed (170/100 mmHg). Despite amlodipine being added to the treatment, no improvement in blood pressure was achieved and malleolar oedema appeared. On admission, physical examination revealed multiple oral ulcers, cutaneous petechial lesions on the lower legs, malleolar oedema, and a grade II systolic murmur on the aortic focus. The blood pressure was 170/90 mmHg. The patient had no uveitis, genital ulcers or thrombophlebitis. Neurological examination was normal. The pathergy test was positive. Laboratory studies revealed a haematocrit value of 34.8%, a haemoglobin level of 11.7 g/dl, a white blood cell count of 4900×10^6 with a normal differential, and an ESR of 89 mm/h. Blood urea was 154 mg/dl (normal 10–50) and creatinine 2.09 mg/dl (normal 0.7–1.4). Total protein was 7.5 g/dl and albumin 3.5 g/dl. Serum immunoglobulins were within normal levels. Serological tests for rheumatoid factor, antinuclear, anti-DNA and antineutrophil cytoplasmic antibody, complement factor C3 and C4,

and cryoglobulins were negative. Urinalysis showed four leucocytes and 30 red blood cells/hpf. The 24 h urinary protein excretion was 3.1 g/day. Chest X-ray and EKG were normal. Renal ultrasonography showed no abnormalities. A sonographic guided renal biopsy was performed, and light microscopy disclosed 19 glomeruli, all of which had an increase in mesangial matrix with an acute inflammatory component. Capillary basement membrane showed a 'double tracked image'. No necrotizing lesions were seen, but a light lymphocytic infiltrate of the interstitium was evident. Tubuli and arteries were normal. Staining with Congo red showed no positive areas. Immunofluorescence staining revealed granular deposits of C3 and IgG on the mesangial areas and capillary basal membranes. Treatment with prednisone (0.5 mg/kg/day) was started and a marked improvement in proteinuria from 3 to 1.5 g/day was evident after 4 weeks of treatment.

The exact frequency of renal involvement in BS is unknown, because only a few cases of renal amyloidosis [2], interstitial nephritis [3] or glomerulonephritis [4, 5] have been reported, and screening for kidney disease is not usually performed. Focal glomerulonephritis with fibrinoid necrosis and crescent formation has been the main form of glomerular disease reported in BS [6], and only rare cases of diffuse proliferative or membranous glomerulonephritis have been described [7, 8]. In our series of 62 patients, only the patient reported has developed renal involvement. This patient presented a rapidly progressive renal insufficiency with severe hypertension, and a simultaneous relapse of oral ulcers and cutaneous vasculitis, which led us to believe that a common underlying mechanism was involved. Light microscopy demonstrated a scarred diffuse proliferative glomerulonephritis, with dense deposits of IgG and C3. Previously, a patient with diffuse proliferative sclerosing glomerulonephritis and predominant deposition of IgM had been reported by Hamuryudan *et al.* [7], and two patients with BS and IgA deposits in the glomerular mesangial areas, indistinguishable histologically from a primary IgA nephritis, were reported by Hamuryudan *et al.* [7] and Hemmen *et al.* [9]. An immune complex-induced physiopathology was postulated for the glomerular lesions, but despite that hypothesis seeming attractive, it is difficult to claim a primary role for autoimmunity. Undoubtedly, detailed studies of additional cases of glomerular involvement are needed for a better understanding of this issue, and systematic nephrological screening of BS patients, including appropriate biopsies, are needed to clarify the real frequency and relevance of kidney involvement in BS.

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1. O'Duffy. Behçet's disease. *Curr Opin Rheumatol* 1994;6:39-43.
2. Yurdakul S, Tuzuner N, Yurdakul I, Hamuryudan V, Yazici H. Amyloidosis in Behçet syndrome. *Arthritis Rheum* 1990; 33:1586-9.
3. Yudis M. Nephropathy with Behçet's syndrome. *Arch Intern Med* 1979;139:602-3.
4. Kansu E, Deghin S, Cantor RI. The expanding spectrum of Behçet's syndrome. *J Am Med Assoc* 1977;237:1855-6.
5. Wilkey D, Yocum DE, Oberley TD, Sundstrom WR, Kare L. Budd-Chiari syndrome and renal failure in Behçet's disease. *Am J Med* 1983;75:541-50.
6. Donnelly S, Jothy S, Barré P. Crescentic glomerulonephritis in Behçet's syndrome—results of therapy and review of the literature. *Clin Nephrol* 1989;31:213-8.
7. Hamuryudan V, Yurdakul S, Kural AR, Ince U, Yazici H. Diffuse proliferative glomerulonephritis in Behçet's syndrome. *Br J Rheumatol* 1991;30:63-4.
8. Olsson PJ, Gaffney E, Alexander RW, Mars DR, Fuller TJF. Proliferative glomerulonephritis with crescent formation in Behçet's syndrome. *Arch Intern Med* 1980;140:713-4.
9. Hemmen T, Perez-Canto A, Distler A, Ofermann G, Braun J. IgA nephropathy in a patient with Behçet's syndrome—case report and review of the literature. *Br J Rheumatol* 1997;36:696-9.

Cervical Spine Fracture in Ankylosing Spondylitis: A Case of 'Auto-fracture'

STR—The risk of fracture of the cervical spine is increased in ankylosing spondylitis (AS) and this may occur after only trivial injury. Although the trauma may be relatively minor, the incidence of neurological deficit is high. We report a case where the only identifiable insult was repeated dystonic neck movements secondary to long-term psychotropic medication.

A 57-yr-old man with a 25 yr history of AS attended out-patients for review. He was a well-controlled schizophrenic who some years earlier had developed intermittent dystonic neck movements secondary to long-term anti-psychotic medication. He said that he had been quite well, but recently had developed tingling in both hands and his walking had become increasingly stiff. Close questioning revealed no history of even minimal trauma, but he mentioned that he was still getting abnormal neck movements. He denied alcohol abuse and there had been no alteration of bladder or bowel function.

Examination revealed a global restriction of spinal movements in keeping with long-standing AS. Neurological examination demonstrated a spastic gait, hypertonia and hyper-reflexia in all four limbs, sensory loss in a C6 distribution, downward plantar responses, and bilateral positive Hoffman's sign. Plain cervical radiology showed the presence of a fracture dislocation at the C6/7 intervertebral disc space, with forward slip of C6 on C7 and slight forward slip of C2 on C3 (Fig. 1). Magnetic resonance scanning confirmed spinal cord compression predominantly at C6/7, and to a minor extent at C2/3. He was referred to the neurosurgeons and underwent anterior plating of C6/7 with neurological improvement. Post-operative X-rays showed little change in the position of the cervical vertebrae and he therefore had a C6 laminectomy with insertion of Hartshill rectangles bridging C6/7 and C2/3 to stabilize the spine. He made an uneventful

recovery with complete resolution of his neurological symptoms.

The risk of spinal fracture is increased in long-standing AS as the fused spine has often become osteoporotic and is vulnerable to trauma [1]. The fractures usually occur in the lower cervical spine and commonly through the C6/7 interspace [2]. The risk of severe neurological impairment (and thus mortality) is related to the site of the fracture. Transdiscal fractures have a limited risk of neurological damage, whereas cases with vertebral body fractures commonly have marked neurological damage, with the degree of neurological damage having a clear relationship to mortality [2]. Patients may give a history of a hyper-extension injury, which may be trivial, and there is often a history of prior alcohol use. Severe neurological deficit occurs in up to 57% of cases and mortality is double that of cervical fractures in the normal population [1, 3].

The association of neuroleptic medication with joint injury has previously been reported [4]. Injury to the cervical spine has also been reported in other conditions, including athetoid cerebral palsy, cervical dystonia (spasmodic torticollis) and congenital muscular torticollis. In severe cases, this can progress to cervical myelopathy [5]. Injury to other parts of the body has been reported in conditions such as myoclonus [6] and severe tardive dystonia [7].

Patients with AS who suffer any kind of spinal trauma or complain of neurological symptoms require urgent clinical and radiological assessment by an



FIG. 1.—Lateral cervical X-ray demonstrating slight forward slip of C2 on C3, and a fracture dislocation at C6/7 with forward slip of C6 on C7.

experienced physician. Undisplaced fractures are difficult to identify because of spinal osteoporosis and the abnormal appearances of the ankylosed spine [8]. Stable fractures should be managed conservatively with rigid immobilization, ideally in a unit experienced in dealing with such fractures [9]. Patients with progressive neurological lesions require neurosurgical intervention [8].

Despite close questioning, our patient was unable to identify any recent injury. In the light of this, we feel it is likely that the cervical fracture was as a result of his dystonic neck movements, and to our knowledge this has not been reported previously. This case emphasizes that patients with AS may incur cervical spine fractures following a minor insult and as patients are often unaware that they have an increased risk of spinal fracture [10], clinicians should therefore be alert to this potentially serious complication.

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1. Murray GC, Persellin RH. Cervical fracture complicating ankylosing spondylitis: a report of eight cases and review of the literature. *Am J Med* 1981;70:1033-41.
2. Harding JR, McCall IW, Park WM, Jones BF. Fracture of the cervical spine in ankylosing spondylitis. *Br J Radiol* 1985;58:3-7.
3. Foo D, Sarkarati M, Marcelino V. Cervical spinal cord injury complicating ankylosing spondylitis. *Paraplegia* 1985;23:358-63.
4. Ibrahim ZY, Brooks EF. Neuroleptic induced bilateral temporomandibular joint dislocation. [Letter] *Am J Psychiatry* 1996; 153:293-4.
5. El-Mallakh RS, Rao K, Barwick M. Cervical myelopathy secondary to movement disorders: case report. *Neurosurgery* 1989;24:902-5.
6. Van Heest A, Vorlicky L, Thompson RC Jr. Bilateral central acetabular fracture dislocations secondary to sustained myoclonus. *Clin Orthop* 1996;324:210-3.
7. Szymanski S, Lieberman JA, Safferman A, Galkowski B. Rib fractures as an unusual complication of severe tardive dystonia. [Letter] *J Clin Psychiatry* 1993;54:160.
8. Hunter T, Dubo H. Spinal fractures complicating ankylosing spondylitis. *Ann Intern Med* 1978;88:546-9.
9. Graham B, Van Peteghem PK. Fractures of the spine in ankylosing spondylitis. Diagnosis, treatment and complications. *Spine* 1989;14:803-7.
10. Wade W, Saltzstein R, Maiman D. Spinal fractures complicating ankylosing spondylitis. *Arch Phys Med Rehabil* 1989; 70:398-401.

Ultrastructural Demonstration of Intracellular

Localization of *Borrelia burgdorferi* in Lyme Arthritis

STR—Lyme arthritis is a common feature of Lyme disease, a multisystem disorder caused by *Borrelia burgdorferi sensu lato* (*B. burgdorferi*) [1]. Its diagnosis, currently based on clinical findings, may be difficult in the absence of typical features, such as erythema chronicum migrans. Furthermore, serological tests are prone to non-specific reactions, and the interpretation

of results in endemic areas may be hampered by asymptomatic infections. Direct detection of the organism in the joint would, therefore, be a major step forward in diagnosis and might also shed light on the pathophysiology of the disease. We report here the first demonstration, to our knowledge, of *B. burgdorferi* in synovial cells of a Lyme arthritis patient using chromosomal DNA detection and ultrastructural study of the synovium.

The patient concerned was a 71-yr-old man from a rural region in the east of France where 11% of the abundant ticks (*Ixodes ricinus*) carry *B. burgdorferi* [2]. He reported developing an erythematous lesion after having been bitten by a tick in March 1991. A physician was not consulted at the time. Acute inflammatory polyarthralgia subsequently developed, followed 2 months later by sensorimotor polyneuropathy affecting the lower limbs, with distal pain, paraesthesiae and stepping gait due to bilateral paralysis of the extensor muscles of the toes. Although neurological signs gradually improved, the patient experienced an attack of arthritis of the knees that had been progressing for 10 days when he was hospitalized in the authors' unit on 16 December 1991. Intravenous ceftriaxone (4 g/day) had been administered for 4 days prior to hospitalization. Physical examination on admission revealed asymmetrical arthritis of the knees, with effusion and a popliteal cyst on the left side. The motor problems had completely regressed, but paraesthesiae and hypoaesthesiae of the feet remained, as did bilateral Achilles areflexia.

Laboratory analysis revealed negative tests for RF and ANA. On serum IgG ELISA using a commercial kit (Enzygnost *Borrelia*, Behring), the titre was 60 U (significant if ≥ 6 U). Western blot (Wb) analysis, performed as previously described [3], gave a positive result according to the criteria currently recommended by the US Centers for Disease Control [4], with IgG bands visible at 15, 18, 28, 30, 41, 45, 52, 56, 68 and 90 kDa. Analysis of cerebrospinal fluid (CSF) revealed a normal cell count and protein level. The leucocyte count in SF was 18 700/mm³, with most cells being of the polymorphonuclear type. SF cultures on the usual media were negative, and no culture was performed on a specific *B. burgdorferi* medium. Plain radiographs of the knees showed minor degenerative changes. Arthroscopic examination confirmed osteoarthritis of the left knee. The synovium appeared inflammatory and hypervascular, with hypertrophic villosity. Several samples were taken for microscopic examination and DNA amplification by polymerase chain reaction (PCR). *Borrelia burgdorferi* DNA was amplified as previously described, using a specific 230 bp segment of the chromosomal flagellin gene as the target [3]. Although no *B. burgdorferi* DNA was detected in SF or CSF, it was detected in SM removed 12 days after the onset of arthritis in the knees.

Synovial fragments for ultrastructural study were fixed in 2.5% glutaraldehyde for 2 h and rinsed thoroughly with cacodylate buffer for 1 h before being post-fixed in 1% aqueous OsO₄ solution for 90 min,

rinsed again in cacodylate buffer, dehydrated, and embedded in Epon. Ultra-thin sections were then stained with uranyl acetate and lead nitrate, and examined using a Philips CM 10 electron microscope.

The synovial sample studied using transmission electron microscopy (TEM) was found to be covered with three or four layers of synoviocytes. The underlying, highly vascular, connective tissue showed mild inflammation.

Several electron-dense filamentous structures, some of which were over 2 μm long and 250 nm wide, were detected in the cytoplasm of fibroblast-like cells of the connective tissue (Fig. 1) and in one macrophage-like synoviocyte (Fig. 2). Dense and fibrillar at the centre, and enclosed by a thick dense envelope separated from the thin outlying membrane by an electrolucent space, they resembled *B. burgdorferi*.

Parenteral treatment with ceftriaxone was restarted in a 3 week regimen of 4 g/day. By February 1992, the peripheral neuropathic symptoms had disappeared, but the patient complained of persistent arthralgia. Clinical examination revealed a popliteal cyst on the left side. Twice-daily treatment with ceftriaxone 2 g was continued for a further 3 weeks. By June 1993, the complaints were limited to bilateral gonalgia; 3 yr later, the symptoms were unchanged.

The diagnosis of Lyme arthritis in the present case was supported by a clinical history suggestive of Lyme disease and by serological testing. Detection of *B. burgdorferi* chromosomal DNA indicated that the organism was probably present in the SM. However, consistent with previous work [3], simultaneous testing of SF was negative. This may be due to sequestration of *B. burgdorferi* in the SM, and explains why chromosomal DNA is less frequently detected in SF than

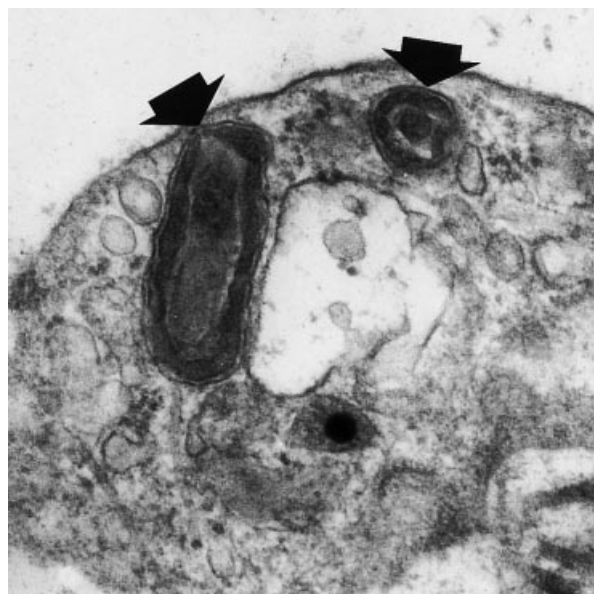
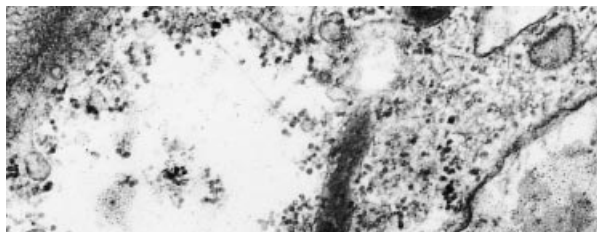


Fig. 2.—TEM of synovial tissue (arthroscopic biopsy of the left knee, 12 days after the onset of arthritis). Transverse sections of the helicoidal bacteria (230 nm wide) appear as free inclusions within a synoviocyte (original magnification $\times 39\,000$).

plasmidic DNA, which may be released into joint fluid from spirochaetes found in the SM [5]. Ultrastructural study confirmed the PCR results and provided further information about the condition and location of the organism.

Since the original study by Johnston *et al.* [6], *B. burgdorferi* has very rarely been reported in the synovium at the light microscope level [7] or by TEM [8, 9]. When it has, the bacteria, or identifiable fragments of them, have been shown to be located in the perivascular regions and among collagen fibres in the deep stroma of the SM. Using immunoelectron microscopy, Nanagara *et al.* [9] also reported finding spirochaetal antigens in the cytoplasmic vacuoles of a fibroblast in a single patient. In the present study, it is important to note the main intracellular location of the organism in the cytoplasm of fibroblast-like cells.

Experimental studies have shown that the spirochaete can penetrate human resident synovial cells and survive there despite exposure to ceftriaxone, which eradicates only extracellular pathogens [10]. The present case suggests that *B. burgdorferi* may also be able to shelter in synovial cells after an incomplete course of antibiotic therapy.

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