Canad. Med. Ass. J.
April 30, 1966, vol. 94

Sclerotic Lesions of Bone in Myeloma

G. R. LANGLEY, M.D., F.R.C.P.[C],* H. B. SABEAN, M.D.† and
K. SORGER, M.D.,‡ *Halifax, N.S.*

ABSTRACT

Osteolytic defects and osteoporosis are common in myeloma, while sclerotic lesions of bone are rare. Eighteen patients with increased bone density have been described in the literature and five patients are presented in this report. Diffuse increase in skeletal density, similar to that seen in the myelofibrosis-myelosclerosis syndrome, occurred in two patients, and progressive multiple focal areas of sclerosis with splenomegaly in a third. Two patients had solitary areas of sclerosis. Although there was increased cortical and trabecular bone, osteoblastic activity was normal on histological sections. Whether the sclerosis was due to new bone formation or interference with bone resorptive processes could not be determined. Patients with polycythemia, myelofibrosis and myelosclerosis have been found to have, or later develop, myeloma. This has led to the suggestion that myeloma be included among the myeloproliferative disorders. At present the evidence for this interrelationship is the frequency of the association of these diseases.

SOMMAIRE

Dans le myélome, on trouve couramment des troubles ostéolytiques et de l'ostéoporose, tandis que les lésions sclérotiques sont rares. La littérature médicale a décrit 18 malades présentant une augmentation de la densité osseuse et le présent rapport traite de cinq malades. Chez deux malades, est survenue une augmentation diffuse de la densité des os du squelette, semblable à celle qu'on observe dans le syndrome myélofibrose-myélosclérose et, chez un troisième, on constatait de multiples foyers de sclérose, à allure progressive, avec splénomégalie. Deux malades présentaient des foyers solitaires de sclérose. Bien qu'il y aît augmentation du cortex et de la zône trabéculée des os, l'examen des coupes histologiques a révélé que l'activité ostéoblastique était normale. Il n'a pas été possible d'établir si la sclérose relevait de l'ostéogénèse ou d'un trouble du mécanisme de résorption des os. On a constaté chez les malades souffrant de polycythémie, de myélofibrose et de myélosclérose, un myélome coexistant ou qui apparaissait ultérieurement. Ceci a porté à croire que le myélome peut être considéré comme appartenant à la classe des troubles myéloprolifératifs. Cette théorie d'interrelation est basée actuellement sur la fréquence d'association de ces pathologies.

ALTHOUGH plasma cell tumours are usually tumours of marrow, their frequent encroachment upon and destruction of bone are well recognized. The radiological manifestations in the skeleton are, however, variable, although the classical radiographic findings consist of innumerable punched-out areas of destruction involving many bones.[1] Osteoporosis particularly involving the spine has been frequently observed either as the sole radiological abnormality or in association with osteolytic lesions.[1, 2] The earlier recognition of myeloma, brought about particularly through the increasing use of serum electrophoresis, has enabled the diagnosis to be established, frequently before radiological changes are evident.[3] The least common bone alteration observed in myeloma is a sclerotic reaction. It is the purpose of this paper to record briefly our findings in five patients in whom a sclerotic reaction of bone was observed in association with myeloma.

From the Departments of Medicine, Radiology and Pathology, Dalhousie University and the Victoria General Hospital, Halifax, Nova Scotia.

*Assistant Professor of Medicine, Markle Scholar in Academic Medicine.

†Instructor in Radiology.

‡Assistant Professor of Pathology. Present address: Mount Auburn Hospital, Cambridge, Massachusetts, U.S.A.

Address reprint requests to: Dr. G. R. Langley, Dalhousie Public Health Clinic, University Avenue, Halifax, N.S.

Case Reports

Case 1

A 53-year-old female school teacher was admitted to the Victoria General Hospital, Halifax, on July 7, 1961, complaining of constipation and tiredness, with pain in the left elbow, left hip and back, of six months' duration. On examination the only abnormal finding was slight sternal tenderness. The laboratory, radiological and pathological findings are summarized in Tables I, II and III. The diagnosis of myeloma was made on the basis of the sternal marrow aspirate, surgical biopsy of the ilium and the finding of a myeloma-type serum protein on electrophoresis. Diffuse sclerosis of bone was observed on skeletal radiographs and confirmed pathologically by surgical biopsy of the ilium.

During the next four years, she continued to have persistent mild bone pain while taking chlorambucil and later prednisone. She remains alive and at work four years following diagnosis.

TABLE I.—LABORATORY FINDINGS

Case	Hemoglobin (g./100 ml.)	Leukocytes (no./mm³ × 10³)	Bone marrow	Calcium (mg.%)	Inorganic phosphorus (mg.%)	Alkaline phosphatase (Bodansky units)	Total serum protein (g./100 ml.)	Serum globulin (g./100 ml.)	Bence Jones protein	Comment
1	11.7	4.4	11% myeloma cells in sternal marrow; dense infiltrate of myeloma cells in iliac marrow	8.5	3.9	33.1	10.5	6.9	Absent	Anomalous gamma globulin 5.8 g./100 ml. on serum electrophoresis. Blood urea nitrogen (BUN) 12 mg.%
2	7.1	3.2	Sternal marrow, 62% myeloma cells	—	—	0.5	12.0	9.4	Absent	Anomalous gamma globulin 8.9 g./100 ml. on serum electrophoresis. Reticulocyte count 9% with erythroblasts in peripheral blood. BUN 13 mg.%
3	13.0	6.9	Lumbar spine and iliac crest marrow normal. Sternal tumour curettings showed tumour to be composed of myeloma cells and paramyloid.	9.4	—	—	7.6	3.7	Absent	No change in serum proteins following irradiation of solitary lesion. Total serum proteins 9.2 g.% and anomalous gamma globulin of 2.5 g.% noted three years after diagnosis. BUN 11 mg.%
4	8.2	24.6	91% myeloma cells in sternal marrow	—	—	—	7.6	3.9	Present	Gamma globulin 28% on serum electrophoresis. 12% primitive plasma cells, 36% mature plasma cells in peripheral blood. BUN 29 mg.%
5	10.5	6.2	Sternal marrow showed 4% mature plasma cells. Iliac crest marrow showed extensive proliferation of myeloma cells	9.2	4.5	7.2	6.6	2.2	Absent	Gamma globulin 24.3 % on serum electrophoresis. BUN 13 mg.%

CASE 2

A 48-year-old housewife was admitted to the Victoria General Hospital on July 25, 1959, complaining of shortness of breath of two months' duration. She had not noted any pain. On examination she appeared ill and was pale. The laboratory, radiological and pathological findings are summarized in Tables I, II and III.

The diagnosis of multiple myeloma was established on the basis of sternal marrow aspirate and serum electrophoresis. Radiological survey of the skeleton revealed diffuse sclerosis. During the next 15 months she required frequent transfusions and showed no response to chlorambucil. She died on October 2, 1960, with pulmonary infection due to *Candida albicans*.

CASE 3

A 74-year-old man was admitted to the Victoria General Hospital on September 9, 1958, with a pain-

TABLE II.—RADIOLOGICAL FEATURES

Case	Sclerosis	Osteolytic lesions	Osteoporosis	Comment
1	Sclerosis involving skull, vertebrae, ribs, pelvis and femora (Figs. 1 and 2)	—	—	Diffuse sclerosis with coarse trabeculae
2	Sclerosis involving skull, vertebrae, ribs, pelvis and femora (Fig. 3)	—	—	Diffuse sclerosis
3	Sclerosis around periphery of sternal osteolytic lesion (Fig. 4)	Large osteolytic defect in manubrium	—	Solitary bone lesion radiologically
4	Sclerosis involving part of third lumbar vertebral body extending into pedicle (Fig. 5)	Extensive osteolytic lesions in skull and a few in right pubic ramus	Marked osteoporosis of lumbar and dorsal vertebrae	Multiple osteolytic lesions and vertebral osteoporosis with solitary sclerotic lesion
5	Focal dense sclerosis in pelvis, sacrum, cervical, dorsal and lumbar vertebrae, right femoral neck and left fifth rib posteriorly (Figs. 6 and 7)	—	—	Radiographs of chest, pelvis and upper femora available beginning 11 and nine years, respectively, prior to diagnosis. Faint rib sclerosis was present 11 years previously, gradually increasing in density during this period. Increase in sclerosis in pelvis occurred over nine years. Radiographs of dorsal spine and upper femora normal 11 years prior to diagnosis. Enlarged spleen noted radiologically at this time

Canad. Med. Ass. J.
April 30, 1966, vol. 94

TABLE III.—PATHOLOGICAL FEATURES

Case	*Specimen*	*Bone marrow*	*Bone*	*Remarks*
1	Left ilium surgical curettings; right ilium trephine biopsy (Figs. 8 and 9)	Dense myelomatous infiltration	Marked osteosclerosis with thickening of trabecular and cortical bone	Approximately 53% of the slide area (Fig. 8) was bone. (Upper limit of normal range for iliac crest: 27%[4].) Osteoblasts present in normal numbers; inconspicuous osteoid seams
2	Autopsy; sternum, femur	Dense myelomatous infiltration	Sternum showed osteoporosis and osteolysis. Femur showed thickening of trabecular and cortical bone	Vertebral and pelvic bone not available for examination. Spleen weighed 340 g. at postmortem examination
3	Sternal curettings (Figs. 10 and 11)	Dense myelomatous infiltration. Paramyloid	No bone present	Homogeneous pale pink staining material which stained atypically for amyloid
4	Sternum, vertebrae (Fig. 12). Pelvis	Extensive myelomatous infiltration of ribs, sternum and pelvis at postmortem examination	Thickened trabecular bone in third lumbar vertebra. Osteolysis and osteoporosis in sternum, pelvis and other vertebrae	—
5	Right ilium trephine biopsy (Fig. 13). Left ilium surgical curettings (Fig. 14)	Myelomatous infiltration	Thickened trabecular and cortical bone	Approximately 38% of slide area (Fig. 13) was bone. (Upper limit of normal range for iliac crest: 27%.[4]) Osteoblasts present in normal numbers. Spleen weighed 1060 g.; sections showed marked extramedullary hematopoiesis (see text)

less sternal swelling of two months' duration. The swelling was seen to arise from the manubrium and was not painful to pressure. Laboratory, radiological and pathological findings are summarized in Tables I, II and III. Radiographs and tomograms of the sternum showed a large osteolytic defect surrounded by a dense sclerotic rim. The lesion was exposed and curetted. On histological examination the curettings consisted of a dense myelomatous infiltrate with a homogeneous pink-staining material which showed atypical staining reactions for amyloid, interpreted as paramyloid deposits. Bone marrow aspirates of iliac crest and lumbar vertebral spine were normal. The lesion was treated with localized radiotherapy and disappeared. This patient remains alive and in a fair state of health six years and nine months following diagnosis. A myeloma-type protein migrating in the gamma$_2$ region, of 2.5 g. %, has been noted since July 1961, although further marrow aspirates have not been done.

CASE 4

A 42-year-old woman was admitted to the Victoria General Hospital on September 28, 1959, complaining of fatigue and pain in the left side of the chest and left tibia. She appeared ill and pale. The laboratory, radiological and pathological findings are summarized in Tables I, II and III. The diagnosis of plasma cell leukemia was made on the basis of the peripheral blood smear, sternal marrow aspirate, and the presence of Bence Jones proteinuria. Radiological examination of the skeleton revealed osteolytic lesions in the skull and pelvis, osteoporosis of the spine, and a solitary dense area of sclerosis in the second lumbar vertebrae. She received frequent transfusions but died six weeks after admission.

CASE 5

A 56-year-old housewife was admitted to the Victoria General Hospital on July 18, 1961, complaining of back pain of six months' duration and a dull aching sternal pain. She had had frequent mild episodes of back pain since 1952, but the present episode was of greater severity. There had been a 25-lb. weight loss over the previous 18 months. She had had several radiographs of the lumbar spine and pelvis because of the back pain over the preceding nine years and these were available for comparison. On examination the liver was 2 cm. below the right costal margin and the spleen was palpable at the left costal margin. The laboratory, radiological and pathological findings are summarized in Tables I, II and III. Focal areas of sclerosis were evident in the fifth rib posteriorly, several vertebrae, both ilia, and the right femoral neck. The diagnosis of multiple myeloma was made on the basis of a surgical biopsy of the sclerotic area in the left ilium. X-ray therapy was given to both ilia. She experienced relief of her low back pain and remained well until March 1965, when fatigue and shortness of breath were noted. The hemoglobin at that time was found to be 6.8 g. %, and the reticulocyte count 28%. The direct Coombs test was positive and the chromium-51 red cell 50% survival of autologous cells was three days. There was marked red cell sequestration of her own cells in the spleen. Splenectomy was performed on April 25, 1965. The histological findings are recorded in Table III. The hemoglobin remained at 11.9 g. % following splenectomy, and the reticulocyte count fell to 1.9%.

DISCUSSION

The absence of skeletal sclerosis in myeloma is familiar. It is reflected in the sharply demarcated lytic lesions without osteoblastic reaction and the usually normal serum alkaline phosphatase.[5] Osteo-

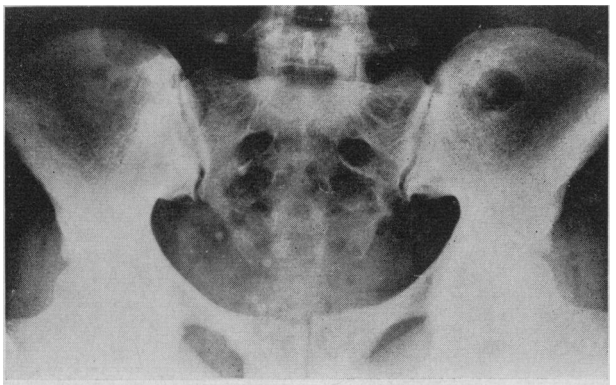

Fig. 1

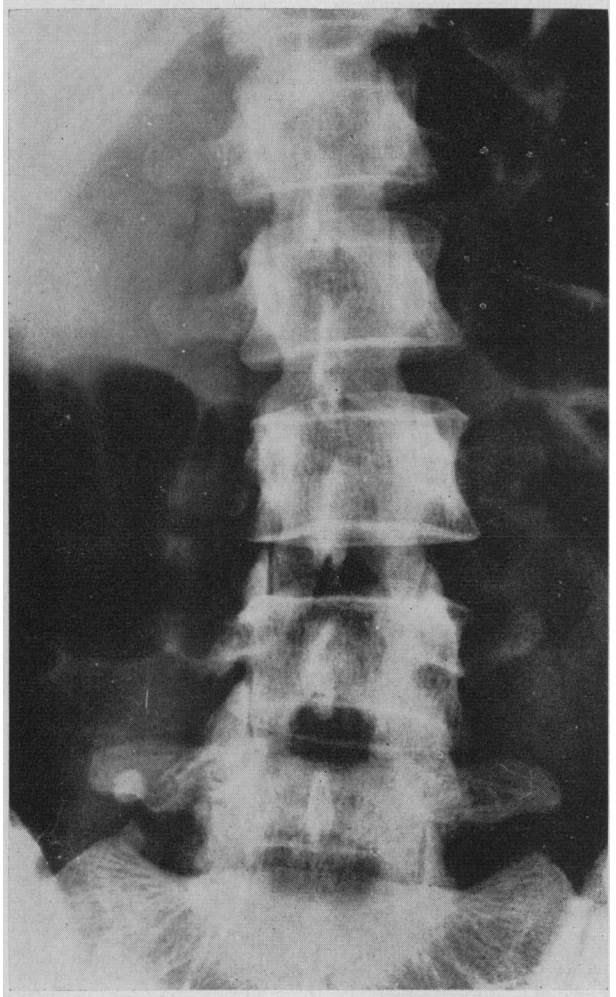

Fig. 2

Figs. 1 and 2.—Case 1. Diffuse sclerosis with a coarse trabecular pattern involving the entire axial skeleton as seen in the lumbar spine and pelvis.

blastic proliferation can occur, however, since adequate callus may form at the sites of pathological fractures, and dense sclerosis has been observed after radiation or other therapy.[6, 7] The occurrence of sclerosis in proved myeloma, in the absence of fracture or therapy, has been recorded in 18 patients,[8-21] in five of whom[11, 13, 18, 20] marked sclerosis was present, similar to Cases 1 and 2 of this series.

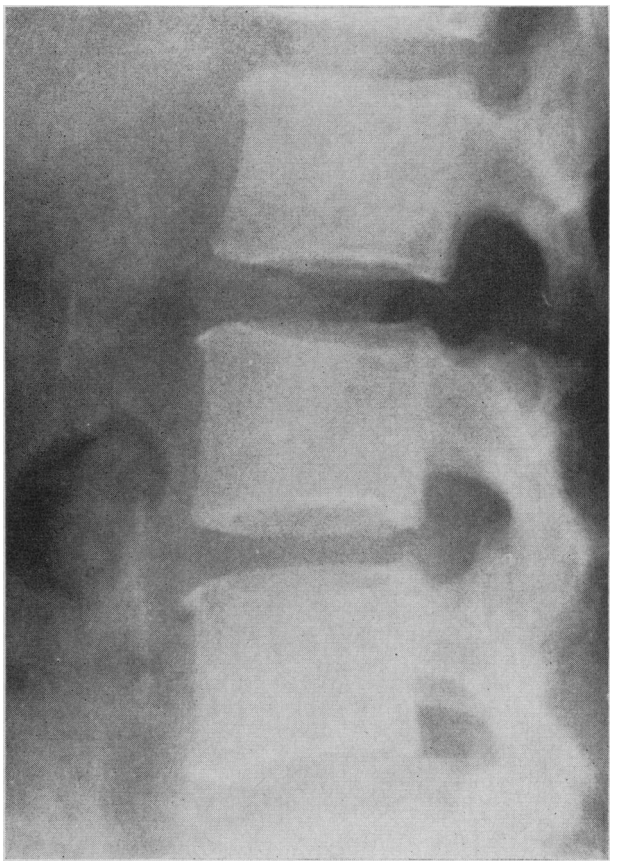

Fig. 3.—Case 2. Diffuse sclerosis with obliteration of trabecular pattern as seen in the lumbar spine; similar changes were seen in the entire axial skeleton of this patient.

More often, however, single or multiple focal areas of sclerosis, as in Cases 3, 4 and 5, sometimes in association with osteolysis, osteoporosis, or spicule formation, have been seen.[8-10, 12, 14-17, 19]

Localized areas of sclerosis in myeloma may occur in the presence of paramyloid. Schinz *et al.*[22] noted that the classical radiological criteria for the diagnosis of plasmacytoma will not pertain if paramyloid is deposited within the tumour. Intensive endosteal and periosteal marginal reaction to an osteolytic lesion may occur with paramyloid.

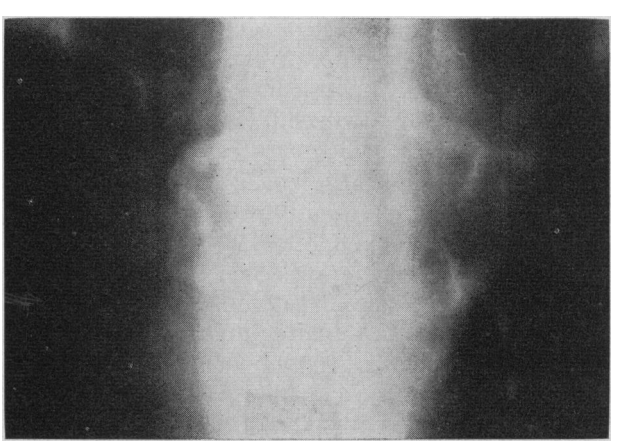

Fig. 4.—Case 3. Tomogram of manubrium sterni showing sclerotic margins and some dense bony struts extending inward from the periphery of an osteolytic lesion.

Canad. Med. Ass. J.
April 30, 1966, vol. 94

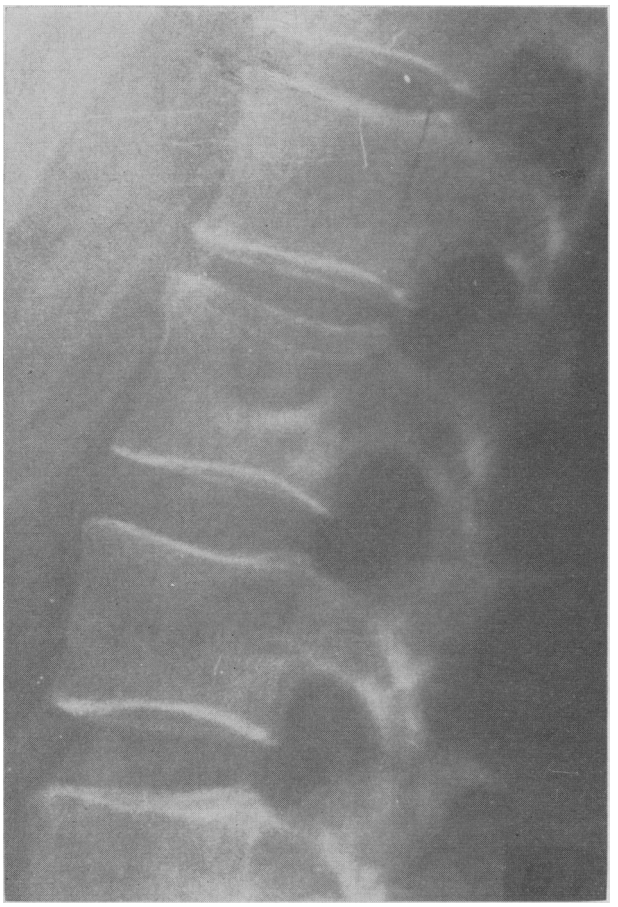

Fig. 5.—Case 4. Solitary density near base of pedicle in lumbar vertebra of an otherwise osteoporotic spine. Classical "punched-out" lesions were present in skull, pelvis and upper femora.

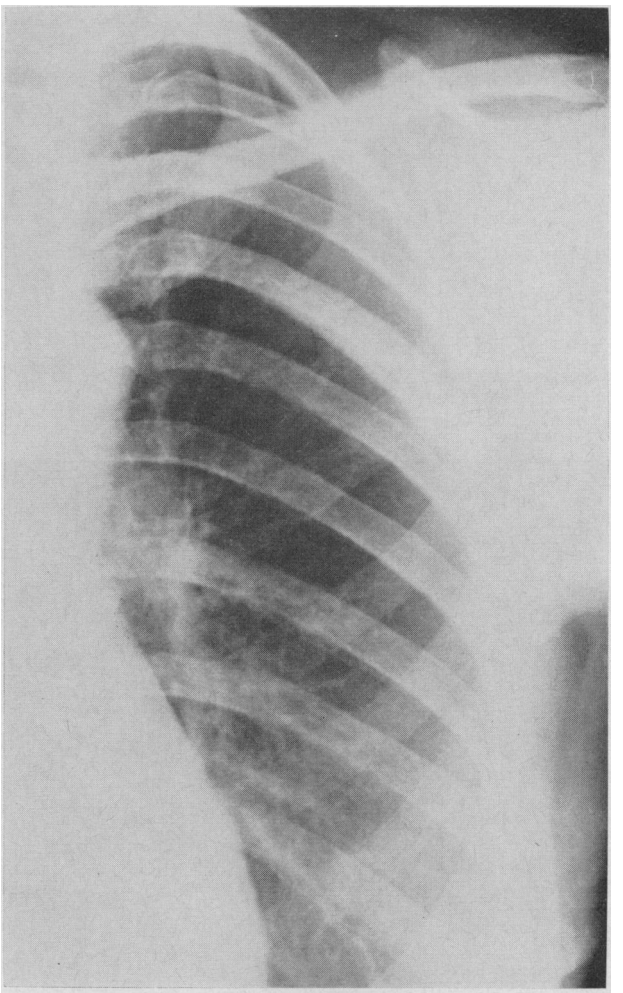

Fig. 6

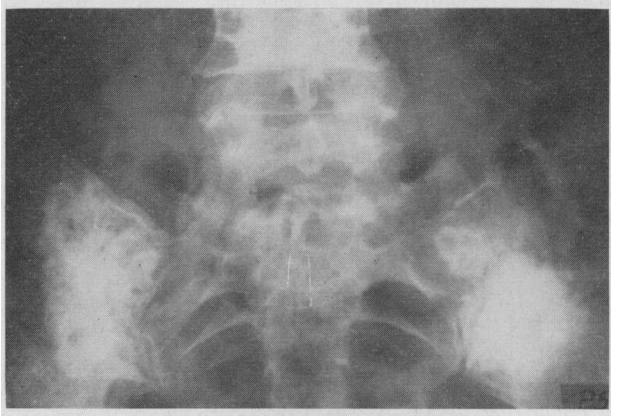

Fig. 7

Figs. 6 and 7.—Case 5. Multiple focal sclerotic lesions as seen in fifth rib, pelvis, sacrum and lumbar spine.

Paramyloid was present in one patient in the present report (Case 3) but was not identified in pathological material from the other four patients.

Multiple myeloma has occurred in association with polycythemia vera and myelofibrosis.[14, 17, 23-25] Although cellular proliferation in myeloma is usually considered to be solely plasmacytic, recent studies by Burston and Pinniger[26] suggest that abnormal marrow fibroblastic proliferation may be common. The association of myeloma with myelosclerosis, myelofibrosis and polycythemia vera has led to the suggestion that myeloma be included among the myeloproliferative disorders, implying that a totipotent stem cell may be capable, under appropriate stimulation, of differentiating into one or more of several cell types.[17, 25]

The overlapping histological features and the anomalous proteins found in multiple myeloma, lymphosarcoma and lymphocytic leukemia suggest that myeloma could be classified in close relationship to the lymphoproliferative states.[27] Azar, Hill and Osserman,[28] in evaluating myeloma-type serum proteins in malignant lymphoma, stated, "It remains to be stressed that intermediate forms exist and overlapping occurs between the lymphatic tumours and plasmacytomas." Thus, while the neoplastic proliferation of plasma cells in myeloma is usually pure, on occasion it may be associated with myeloproliferative disorders or it may have features in common with a lymphoproliferative disorder.

The concept of myeloma as a myeloproliferative disorder would indicate that the sclerosis of bone in these patients was the result of a simultaneous proliferation of bone-forming elements leading to increased bone deposition.[17] However, in the four

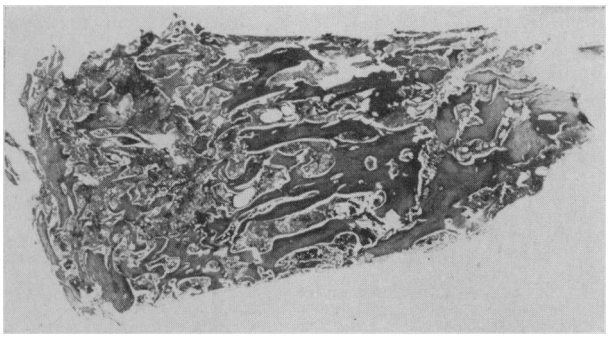

Fig. 8.—Total view of right ilium trephine biopsy in Case 1. There is approximately a two-fold increase of bony tissue beyond the normal range (approximately 53% of the slide area is bone—upper limit of normal range 27%[4]). (H & E; × 5.)

patients in our series in whom bone was available for examination, there was no histological evidence of active bone formation. The serum alkaline phosphatase was elevated in one patient but was normal

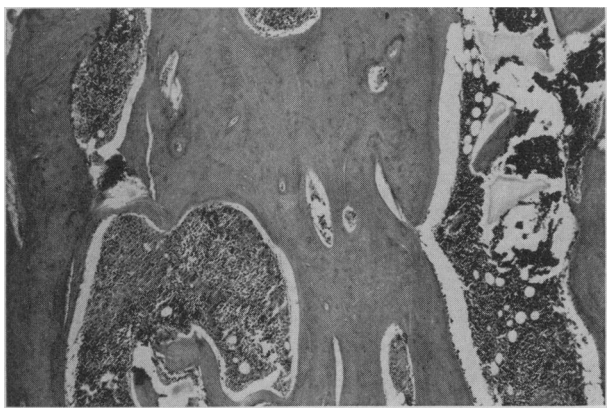

Fig. 9.—Higher magnification of Fig. 8, demonstrating fairly orderly lamellar arrangement of greatly thickened trabecular bone. Osteoid seams are not conspicuous and there is no apparent increase in the number and activity of osteoblasts. The bone marrow is completely replaced by myeloma cells. (H & E; × 100.)

in two others. Therefore, the possibility of some other mechanism, such as interference with the normal resorptive processes of bone, possibly as a result of neoplastic infiltration of the marrow

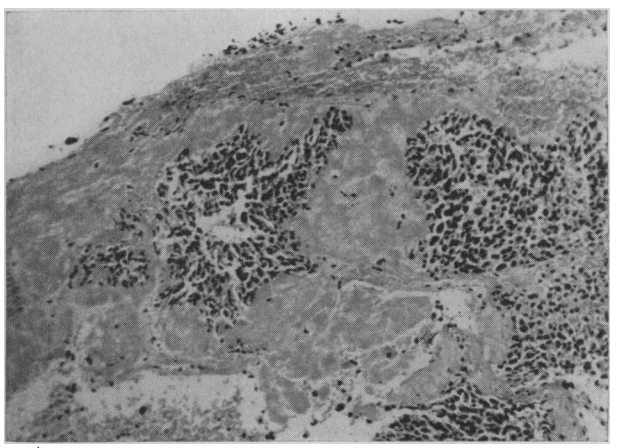

Fig. 10.—Case 3. Sternal curettings showing dense infiltration by myeloma cells and deposits of paramyloid. (H & E; × 300.)

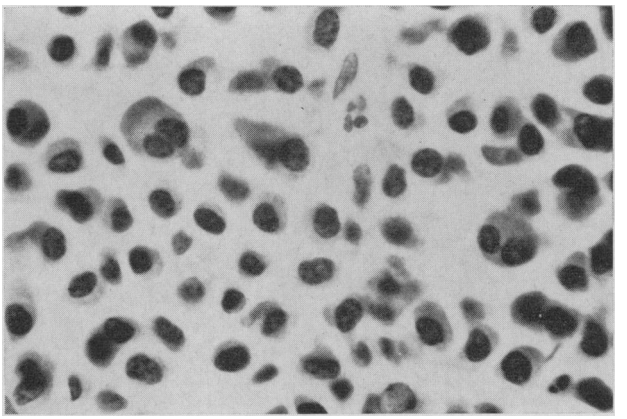

Fig. 11.—High-power view of same Case (3) demonstrating cytologic detail of myeloma cells. (× 1125.)

spaces, cannot be excluded as a cause of the osseous sclerosis.

In Case 5 there was progressive sclerosis of bone during the 11 years prior to the histological diagnosis of myeloma, and splenomegaly was present during this period. Although there were neither morphological red cell changes nor immature erythroid or myeloid elements in the peripheral blood, the bone sclerosis and splenomegaly suggested a myeloproliferative disorder. However, long survivals have been recognized in myeloma,[29, 30] and it is therefore possible that myelomatous cell proliferation was present from the beginning.

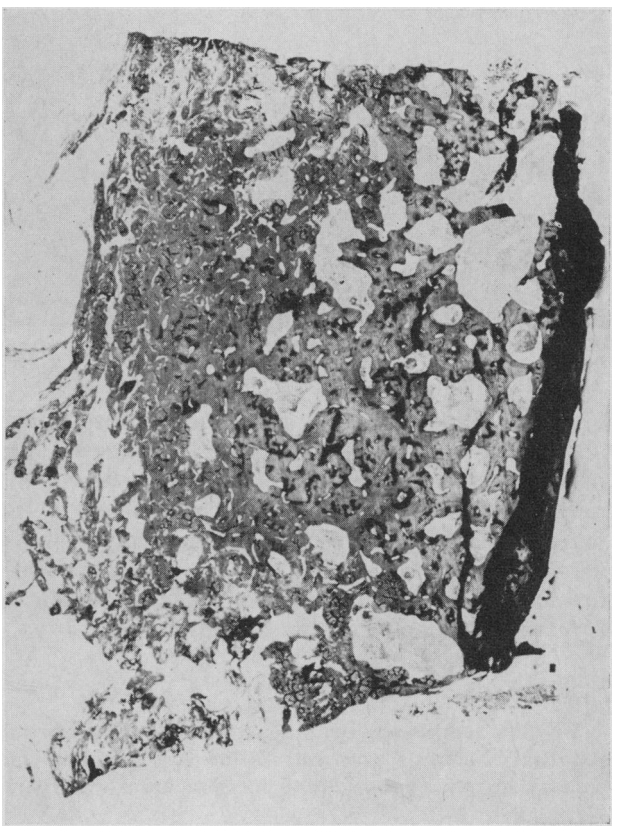

Fig. 12.—Low-power view of the body of third lumbar vertebra in Case 4 showing marked sclerosis of trabecular and cortical bone. (H & E; × 5.)

Canad. Med. Ass. J.
April 30, 1966, vol. 94

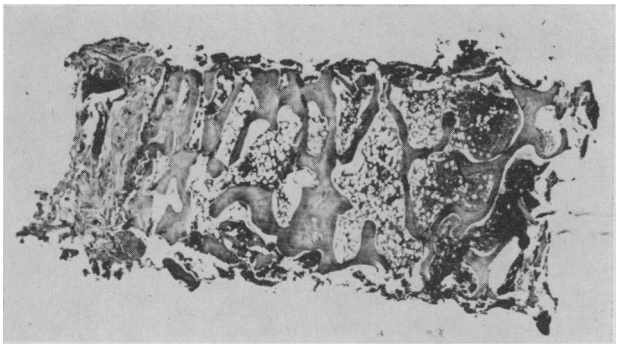

Fig. 13.—Total view of iliac trephine biopsy in Case 5 showing partial replacement of the normal marrow by myeloma cells and marked patchy thickening of trabecular bone (approximately 38% of slide area is bone—upper limit of normal range for iliac crest 27%[4]). (H & E; × 5.)

Bone sclerosis can be observed in a vast number of diseases[31] in addition to myeloma, and it is important to determine whether there was a coincidental association of sclerosis in these patients with myeloma or if there was some relationship between the two processes. It is not possible to exclude the former completely or to provide unequivocal evidence of the latter. The clinical features and the pathological material, including autopsies in two patients, did not suggest alternative diagnoses.

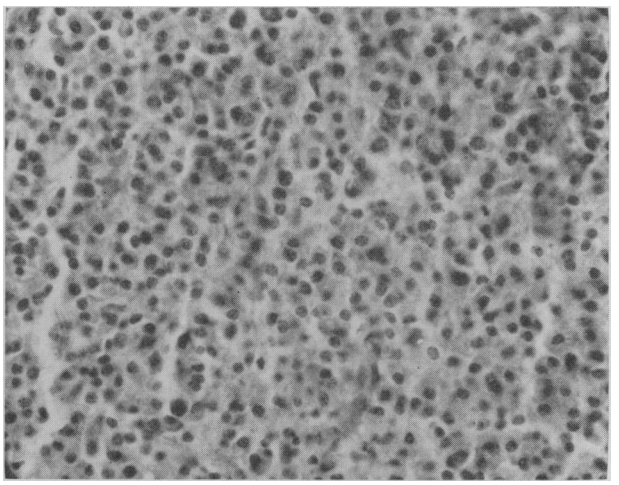

Fig. 14.—Case 5: Myelomatous infiltration in marrow of left ilium. (× 500.)

Fluoride intoxication was excluded because of the absence of typical radiological changes[32] and normal fluoride levels in the drinking water of the patients.* The frequency of the association of the other myeloproliferative disorders, polycythemia vera, myelofibrosis and myelosclerosis, with myeloma is at present the best evidence favouring a relationship between the two processes.

SUMMARY

Five patients with bone sclerosis and myeloma are reported. Sclerosis was diffuse in two patients and solitary in two (one of these in association with paramyloid), and in one patient multiple focal areas of sclerosis were seen. The relationship of this type of bone lesion to myeloma is discussed.

We wish to thank Drs. H. C. Read and D. J. Tonning for permission to study patients under their care.

*Information kindly provided by Dr. W. C. King, Department of Health, Nova Scotia Government. Fluoride levels were found to range from 0.04 to 0.9 p.p.m.

REFERENCES

1. SNAPPER, I., TURNER, L. B. AND MOSCOVITZ, H. L.: Multiple myeloma, Grune & Stratton Inc., New York, 1953.
2. HEISER, S. AND SCHWARTZMAN, J. J.: *Radiology*, **58**: 178, 1952.
3. OSSERMAN, E. F.: *Ibid.*, **71**: 157, 1958.
4. BECK, J. S. AND NORDIN, B. E. C.: *J. Path. Bact.*, **80**: 391, 1960.
5. MARTIN, N. H. AND SCULTHORPE, H.: *J. Clin. Path.*, **11**: 330, 1958.
6. BAILEY, C. O.: *Amer. J. Roentgen.*, **36**: 980, 1936.
7. COHEN, P. AND GARDNER, F. H.: *New Eng. J. Med.*, **271**: 1123, 1964.
8. KRAININ, P., D'ANGIO, C. J. AND SMELIN, A.: *Arch. Intern. Med. (Chicago)*, **84**: 976, 1949.
9. KOHLER, L. M. AND LAUR, A.: *Fortschr. Roentgenstr.*, **72**: 714, 1950.
10. BIONDETTI, P.: *Radiol. Med. (Torino)*, **38**: 1076, 1952.
11. SHARNOFF, J. G., BELSKY, H. AND MELTON, J.: *Amer. J. Med.*, **17**: 582, 1954.
12. GALGANO, A. R.: *Amer. J. Roentgen.*, **74**: 304, 1955.
13. VIDEBAEK, A.: *Acta Med. Scand.*, **153**: 459, 1956.
14. HODLER, J.: *Schweiz. Med. Wschr.*, **88**: 1065, 1958.
15. LEWIN, H. AND STEIN, J. M.: *Amer. J. Roentgen.*, **79**: 630, 1958.
16. ODELBERG-JOHNSON, O.: *Acta Radiol. (Stockh.)*, **52**: 139, 1959.
17. SPICKARD, A.: *Bull. Hopkins Hosp.*, **107**: 234, 1960.
18. ENGELS, E. P., SMITH, R. C. AND KRANTZ, S.: *Radiology*, **75**: 242, 1960.
19. PORTER, E. C.: *Ibid.*, **76**: 457, 1961.
20. VAN LESSEN, H. AND GELLISSEN, K.: *Z. Krebsforsch.*, **60**: 200, 1961.
21. FAIRLEY, G. H., JACKSON, D. C. AND MCDONALD, P.: *Brit. J. Radiol.*, **37**: 852, 1964.
22. SCHINZ, H. R. *et al.*: Roentgen diagnostics, vol. 2, edited by J. T. Case, Grune & Stratton Inc., New York, 1952, p. 957.
23. LAWRENCE, J. H. AND ROSENTHAL, R. L.: *Amer. J. Med. Sci.*, **218**: 149, 1949.
24. GIERTSEN, J. C.: *Acta Path. Microbiol. Scand.*, **38**: 439, 1956.
25. BRODY, J. I., BEIZER, L. H. AND SCHWARTZ, S.: *Amer. J. Med.*, **36**: 315, 1964.
26. BURSTON, J. AND PINNIGER, J. L.: *Brit. J. Haemat.*, **9**: 172, 1963.
27. HAYHOE, F. G. J.: Leukemia research and clinical practice, J. & A. Churchill Ltd., London, 1960.
28. AZAR, H. A., HILL, W. T. AND OSSERMAN, E. F.: *Amer. J. Med.*, **23**: 239, 1957.
29. VIDEBAEK, A. AND JOHANSEN, H.: *Danish Med. Bull.*, **3**: 174, 1956.
30. KENNY, J. J. AND MOLONEY, W. C.: *Ann. Intern. Med.*, **45**: 950, 1956.
31. ERF, L. A. AND HERBUT, P. A.: *Ibid.*, **21**: 863, 1944.
32. STEVENSON, C. A. AND WATSON, A. R.: *Amer. J. Roentgen.*, **78**: 13, 1957.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE COMMUNITY SHOULD BEAR THE EXPENSE

In connection with vaccination it appears to me that in view of the fact that the Act makes it compulsory for school children to be vaccinated before attending school, this operation should be offered free to the public generally whether in a position to pay for it or not. At present the Act simply calls for free vaccination by the health officer to those unable to pay for it. In Edmonton our custom has been to vaccinate free of charge all who apply, irrespective of whether they are in good circumstances or not, and as a result of this a great deal of the prejudice against vaccination has been eliminated. In any case, vaccination is a purely public health measure and is intended as a protection to the community at large against smallpox. The community at large, therefore, in my opinion, should bear the expense, not the individual.—T. H. Whitelaw, *Canad Med. Ass. J.*, 6: 317, 1916.