Unusual presentation of multiple myeloma

A report of 2 cases

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Summary

The diagnosis of multiple myeloma (overt plasma cell dyscrasia) is usually not considered in patients under 30 years of age. Furthermore, multiple myeloma with coexistent megaloblastic and iron deficiency anaemia is very uncommon. Within 6 months we encountered 2 patients under 30 years of age who had multiple myeloma, one with advanced secondary amyloidosis and the other with severe megaloblastic and iron deficiency anaemia.

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At the time of diagnosis of multiple myeloma the mean age of patients is reported to be 62 years.[1] Less than 2% of patients with multiple myeloma are below the age of 40 years, and very few well-documented cases in patients below the age of 30 years have been reported.[2]

The pathological features of multiple myeloma or overt plasma cell dyscrasia include the following:[3] (*i*) local or widespread proliferation of B-type lymphocytes; (*ii*) excessive production of one of the monoclonal types of immunoglobulin or its subunits, viz. heavy or light chains; and (*iii*) often decreased production of normal immunoglobulins. These factors have to be considered in the diagnosis of multiple myeloma or overt plasma cell dyscrasia when an abnormal band is detected on serum protein electrophoresis. Special investigations such as bone marrow aspiration, biopsy, comprehensive radiographic skeletal studies and relevant biochemical determinations on blood and urine samples will then establish the diagnosis.

Case reports

Case 1

A 25-year-old Black man (Fig. 1) was referred from a rural hospital complaining of having had painless swellings below the tongue and over both parotid glands for 'many years'. On examination bilateral enlargement of the parotid and submandibular salivary glands and submental lymph nodes was noted. The tongue was hard and enlarged with limited mobility, and an epulis was present in the anterior mandibular sulcus.

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Radiographic studies showed destruction of T7 and lytic lesions in the right parietal area of the skull, the posterior part of the right sixth rib and right ischium and pubis. There was also erosion of the anterior surface of L4. In view of the radiographic findings the following differential diagnoses were considered: lymphoma with bony and soft-tissue infiltration, multiple myeloma and histiocytosis X. The relevant biochemical and haematological findings are shown in Tables I and II respectively.

Serum protein electrophoresis showed a faint monoclonal peak in the early γ area with normal IgG, IgA and IgM levels. Bence Jones protein was present in the urine. The serum and urine immuno-electrophoretic patterns are shown in Fig. 2. IgG,

TABLE I. RELEVANT BIOCHEMICAL FINDINGS IN CASE 1

	Patient's values	Normal ranges
Serum		
Urea (mmol/l)	4,1	2,5 - 6,7
Creatinine (μmol/l)	70	53 - 97
Uric acid (mmol/l)	0,42	0,1 - 0,5
Total protein (g/l)	67	60 - 80
Albumin (g/l)	38	26 - 52
Magnesium (mmol/l)	0,65	0,75 - 1,25
Total calcium (mmol/l)	1,94	2,25 - 2,70
IgG (g/l)	12,0	6,4 - 13,5
IgA (g/l)	1,2	0,7 - 3,12
IgM (g/l)	0,75	0,56 - 3,5
Urine		
Total protein (g/l)	42	< 0,08

TABLE II. RELEVANT HAEMATOLOGICAL FINDINGS IN CASE 1

	Patient's values	Normal ranges (males)
WBC	$7,8 \times 10^9$/l	$7,5 \pm 3,5 \times 10^9$/l
RBC	$4,2 \times 10^{12}$/l	$5,8 \pm 1,0 \times 10^{12}$/l
Hb (g/dl)	12,2	$16,4 \pm 2,5$
MCV (fl)	91,0	$85,0 \pm 8,0$
MCH (pg)	29,0	$29,5 \pm 2,5$
Differential count (%)		
Polymorphs	40	40 - 75
Lymphocytes	58	20 - 45
Monocytes	2	2 - 10
Platelets	365×10^9/l	$150 - 400 \times 10^9$/l
Reticulocytes (%)	4,0	0 - 2
ESR (mm/h)	45 (Wintrobe)	0 - 20

WBC = total white cell count; RBC = red cell count; Hb = haemoglobin concentration; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; ESR = erythrocyte sedimentation rate.

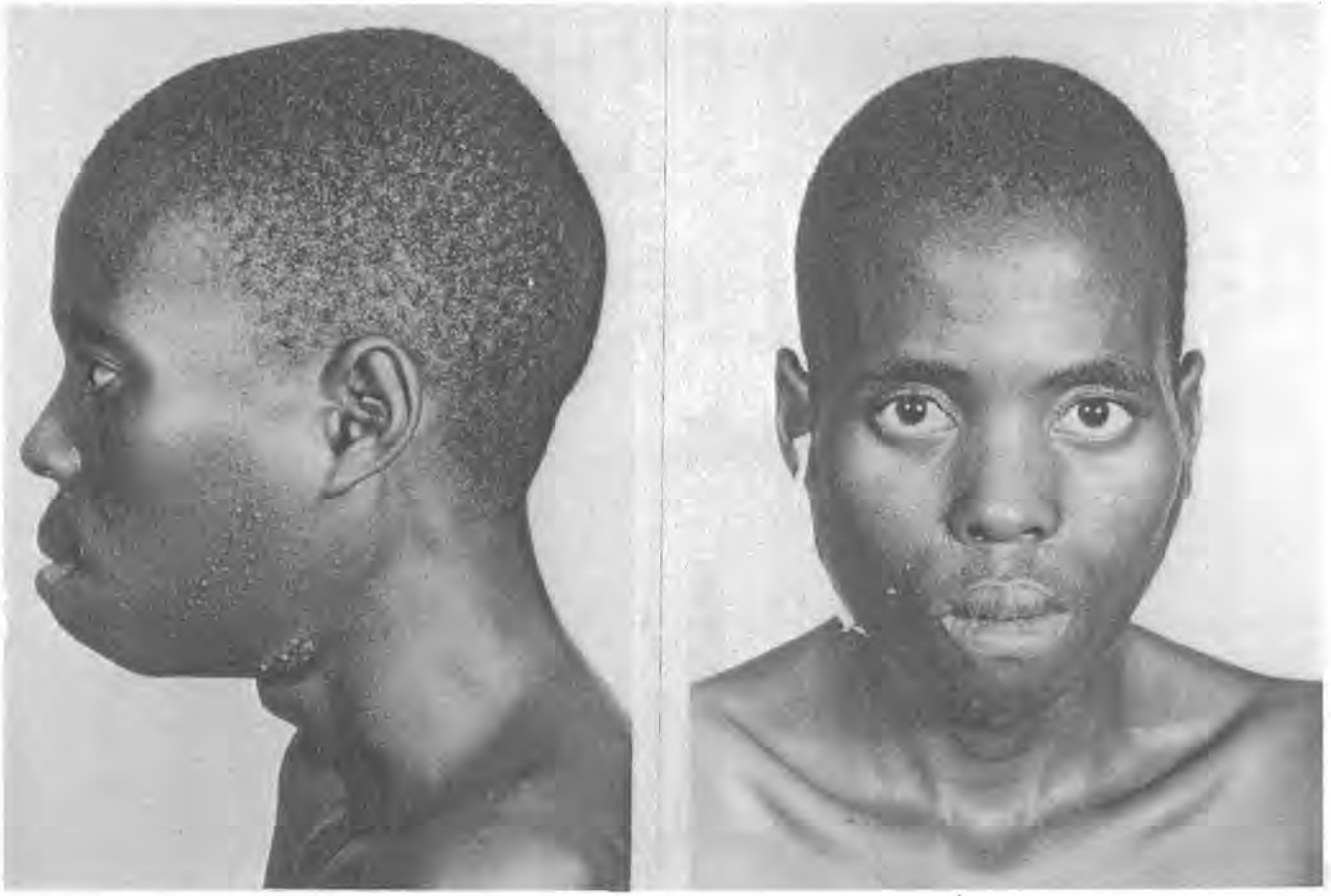

Fig. 1. Patient 1 — frontal and lateral views showing enlargement of the parotid and submandibular salivary glands.

IgA and IgM as well as κ and λ light chains were present in the serum, while immuno-electrophoresis of the urine showed the presence of κ chains identical to those in the serum and also a smaller number of λ chains.

Microscopic examination of both bone marrow aspirate and a biopsy specimen showed a 40% diffuse infiltrate of pleomorphic plasmacytoid cells. Immunoperoxidase staining (Immunolok Histoset, Immunolok Inc.; Carpinteria, USA) of bone marrow sections showed the presence of κ light chains in the cytoplasm of the plasma cells.

The tongue, parotid gland and intra-oral epulis showed extensive deposits of amyloid, this reacting positively with methyl violet and Congo red stains. Numerous dilated capillaries and patchy infiltrates of foamy histiocytes and giant cells were present in the deposits.

On the basis of the radiological, haematological and biochemical findings the diagnosis of multiple myeloma with secondary amyloidosis was made and a course of chemotherapy was instituted.

Case 2

A 26-year-old Black male patient was seen in the casualty department of Ga-Rankuwa Hospital, Pretoria, in a comatose condition with generalized oedema. Since 1981 he had been treated at an outside clinic with thioridazine hydrochloride for a 'psychiatric condition'. On examination the patient responded to pain only. The pulse rate was 100/min and the blood pressure was 90/50 mmHg. The patient had deep, sighing breathing with bilateral rhonchi. Multiple petechial haemorrhages were present all over the body. The patient was then admitted to the intensive care unit.

A full blood count revealed severe macrocytic normochromic anaemia and a leuco-erythroblastic reaction, and blood gas analysis showed the presence of metabolic acidosis (Tables III and IV). On the basis of the haematological findings bone marrow aspiration was performed before packed red blood cells

TABLE III. RELEVANT HAEMATOLOGICAL FINDINGS IN CASE 2

	Patient's values	Normal ranges (males)
WBC	6,1 x 10^9/l (corrected)	7,5 ± 3,5 x 10^9/l
RBC	0,43 x 10^{12}/l	5,8 ± 1,0 x 10^{12}/l
Hb (g/dl)	1,9	16,4 ± 2,6
MCV (fl)	156	85 ± 8
MCH (pg)	46	29,5 ± 2,5
Differential count (%)		
Polymorphs	60	40 - 75
Lymphocytes	26	20 - 45
Monocytes	1	1 - 10
Eosinophils	1	1 - 6
Promyelocytes	5	
Myelocytes	2	
Metamyelocytes	2	
NRBC/100 WBC	18	
Megaloblasts present		
Platelets	10 x 10^9/l	150 - 400 x 10^9/l
Reticulocytes (%)	1,5	0 - 2

NRBC/100 WBC = nucleated red blood cells/100 WBC.

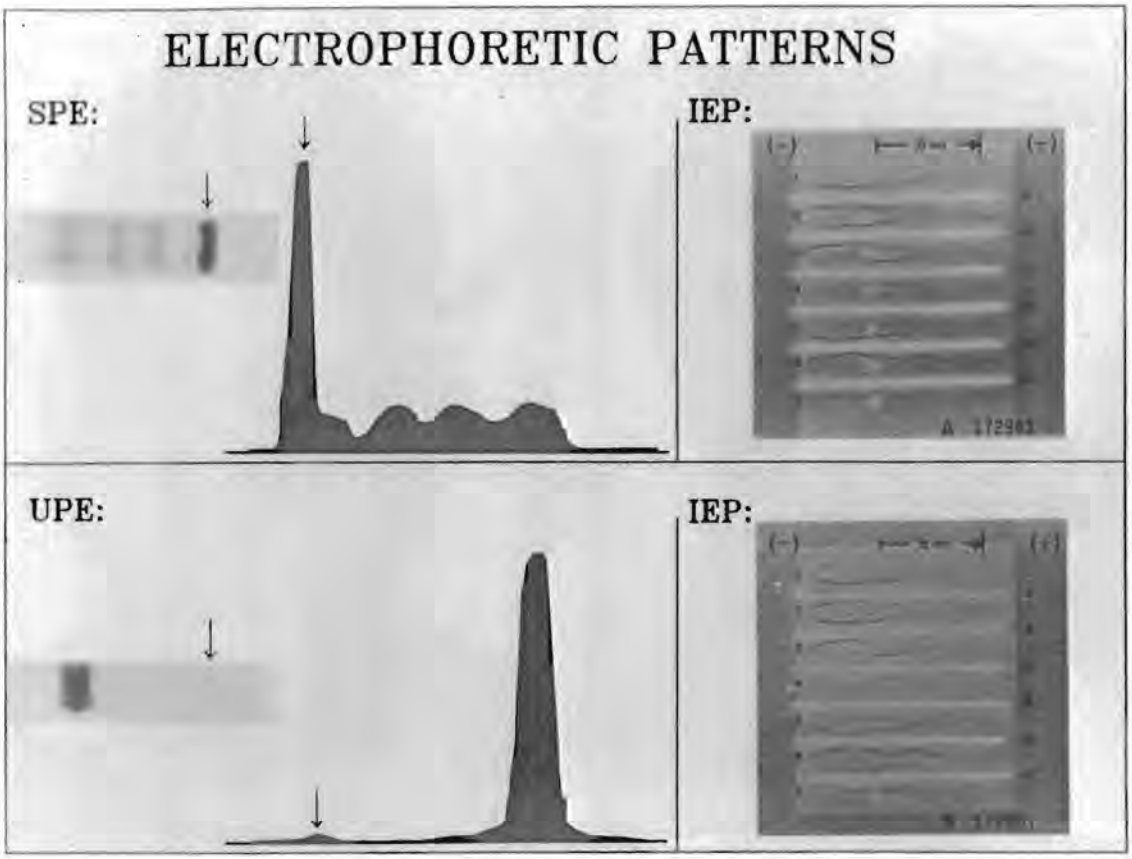

Fig. 2. Serum and urine electrophoretic patterns (SPE and UPE respectively) as well as densitrometric scans of case 1 appear on the left. The peaks (arrows) reflect albumin. On the right, immuno-electrophoretic membranes on both serum (top) and urine (bottom) are shown. In both cases the patients' specimens were put in the wells with even numbers, while control serum was used in the unevenly numbered wells. Antisera were placed in the troughs as follows: A = polyvalent; B = anti-IgG; C = anti-IgA; D = anti-IgM; E = anti-κ; F = anti-λ.

TABLE IV. BIOCHEMICAL FINDINGS AVAILABLE IN CASE 2

	Patient's values	Normal ranges
Serum		
Urea (mmol/l)	11,4	2,5 - 6,7
Creatinine (μmol/l)	172	53 - 97
Arterial blood		
pH	7,45	7,35 - 7,45
P_{CO_2} (kPa)	2,09	4,67 - 6,00
P_{O_2} (kPa)	10,09	10,00 - 13,33
HCO_3 (mmol/l)	10,9	20 - 26
Total CO_2 (mmol/l)	11,3	24,5 - 30,0
Base excess (mmol/l)	−12,0	−3,0 - +1,0
O_2 saturation (%)	94,5	96 - 100
IgG (g/l)	58,4	6,4 - 13,5
IgA (g/l)	0,17	0,7 - 3,12
IgM (g/l)	0,47	0,56 - 3,5

were transfused. Despite treatment for cardiac failure and pulmonary oedema the patient never regained consciousness and died within a few hours. Consent for performance of an autopsy could not be obtained.

The bone marrow showed marked hypercellularity without stainable iron and decreased erythropoiesis and granulopoiesis. The majority of the red cell precursors were megaloblastic and there was a 50% plasma cell infiltrate. On account of the bone marrow findings the small amount of serum available was used for serum protein electrophoresis. An abnormal monoclonal band was found in the early γ area with immunoparesis. The immunoglobulin levels are shown in Table IV. Immuno-electrophoresis of the serum showed the presence of IgG and κ light chains. The diagnosis of megaloblastic and iron deficiency anaemia with multiple myeloma was made.

Discussion

Case 1 demonstrated that serum protein electrophoresis has certain pitfalls, since the faint monoclonal band could be mistaken for an oligoclonal gammopathy.[4] Furthermore, there was no immunoparesis and the age of the patient was far below the expected mean age of 62 years. It was only after examination of the urine for Bence Jones protein, radiographic studies and bone marrow aspiration and biopsy that the diagnosis of multiple myeloma could be made.

The amyloid deposits were suggestive of a pattern I distribution;[3] this principally involves the tongue, gastro-intestinal tract, skin, nerves, muscles and carpal ligaments and is frequently seen in multiple myeloma-related amyloidosis. κ light chains were demonstrated in the plasma cells, serum and urine of this patient. Isobe and Osserman[5] found λ light chains in 50 patients with pattern I amyloid distribution.

The demonstration of multiple myeloma in case 2 was unexpected. A leuco-erythroblastic reaction is rare and is seen in association with heavy infiltration of the bone marrow by neoplastic disease, including multiple myeloma.[6] The patient's sudden death prevented us from establishing the cause of the

megaloblastic anaemia. Larsson[7] has described the coexistence of multiple myeloma and pernicious anaemia, and Di Bisceglie and Hodkinson[8] have reported a similar occurrence in a Black patient aged 72 years. However, our patient was not of that age group. Hoffbrand *et al.*[9] described mild megaloblastic changes in patients with myeloma due to vitamin B_{12} or folate deficiency, but none of his patients showed 'florid megaloblastic changes seen in severe megaloblastic anaemia'. Since our patient had severe megaloblastic anaemia, he may have had a combined deficiency.

In conclusion, the fact that 2 patients below the age of 30 years with multiple myeloma were encountered within a period of 6 months suggests that this disease may occur at a much earlier age in Black patients.

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Tumours of accessory parotid glands

Case reports

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Summary

Tumours arising in accessory parotid glands are a distinct entity and a pitfall for the unwary. The diagnosis is made on the basis of clinical examination and a high index of suspicion is essential. Treatment is by wide exposure and careful dissection because of the relationship of the accessory parotid gland to the facial nerve and parotid duct. Four cases are described.

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The accessory parotid gland is recognized as a distinct entity in the *Nomina Anatomica.* It can be described as salivary tissue adjacent to the parotid duct (Stensen's duct) and separate from the main body of the gland[1] to distinguish it from an anterior facial process, which is parotid tissue extending anteriorly from the main gland but remaining in continuity with it.

Lesions arising in accessory parotid tissue are well described, not all that uncommon, and very often misdiagnosed. During the past 2 years we have treated 4 patients with such lesions.

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Case reports

All the lesions occurred in adult patients between the ages of 25 and 35 years; 2 patients were male and 2 female. The patients presented with a mid-cheek, painless nodule about 1 - 2 cm in diameter and lying deep to the skin just below the zygomatic arch, and easily felt against the tensed masseter muscle. Sialography performed on 3 patients did not demonstrate a lesion.

Anatomy

In order to prevent damage to vital structures at operation it is important to understand the anatomy of the accessory parotid gland. It always lies between the zygomatic (buccal) branch of the facial nerve (above) and the parotid duct (below). One or more fine ducts drain the accessory gland and enter the parotid duct (Fig. 1).

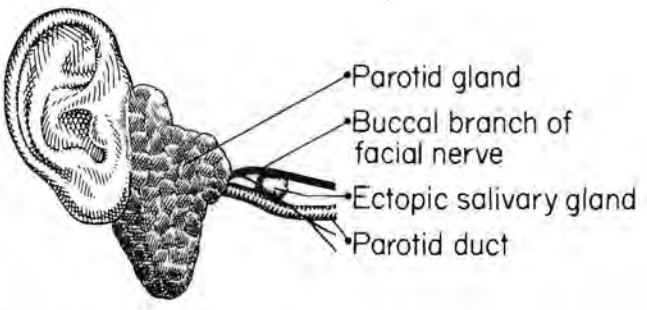

Fig. 1. Anatomical relations of the accessory parotid gland.

MULTIPLE MYELOMA PRESENTING AS A SOLITARY EXPANSILE MANDIBULAR TUMOR

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SUMMARY

A case of multiple myeloma of the mandible presenting as a solitary expansile lesion is reported. Factors influencing the diagnosis and prognosis of the disease are discussed and a multidisciplinary approach to the diagnosis of suspected cases emphasized. The unexpected finding of crystalline inclusions in the nuclei of neoplastic plasma cells demonstrated by ultrastructural examination is considered.

INTRODUCTION

Mutliple myeloma (M.M.) is characterized by a neoplastic proliferation of one or more clones of plasma cells. The disease occurs most frequently in the 6th and 7th decades of life[1,2] and the neoplastic plasma cells synthesize monoclonal immunoglobulins or subunits thereof (heavy or light chains) which may be detected in serum even before lesions become clinically apparent.[1,3] If abnormal light chains are produced they are excreted in urine as Bence Jones proteins, causing renal tubular damage and eventually renal failure.[2] Additional laboratory findings include normocytic normochromic anemia,[2] raised erythrocyte sedimentation rate (ESR), thrombocytopenia[4] and immunoparesis.[2] Furthermore, excessive light chain production leads to amyloid deposits in soft tissues and organs[5] in 6-16% of patients with M.M.[6]

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Oral Manifestations of M.M.

In a radiographic and case record survey of 59 cases, Bruce and Royer[7] found jaw involvement in 17 patients with M.M. A more recent study showed that the incidence of jaw involvement may even be higher.[8] Jaw lesions are more commonly found in the mandible[7,9] and are associated with areas of hemopoiesis, namely the premolar- and molar regions and the ascending ramus.[7,9,10]

The typical radiographic appearance is that of multiple radiolucent lesions with round, well defined, non-corticated borders.[11] Rarely, diffuse involvement of the jaws occur with a radiographic appearance of osteoporosis. Root resorbtion of associated teeth is characteristically absent[12] and mandibular lesions may be associated with pathologic fractures.[13] Common oral symptoms include pain, swelling, numbness of the jaw, mobility of teeth and soft tissue tumors.[10] Enlargement of the tongue and salivary glands are the result of amyloid deposits.[12]

We report a case with multiple myeloma of the mandible which presented as a solitary expansile tumor.

CASE PRESENTATION

A female patient, 70 years of age, was admitted from a rural hospital with a history of a rapid increasing swelling and paresthesia of the lower jaw. She was in a poor systemic condition with a hemoglobin value of 6 g/dℓ for which whole blood infusion was administered.

A soft swelling was present over the lower third of her face. (Fig. 1). A large indurated tumor (10 x 6 cm) extended along the length of the corpus of the mandible breaking the lip seal and protruding extra-orally. Displaced teeth and consequent traumatic ulcerations were present on the mucosa

Fig. 1: Clinical appearance of mandibular tumor.

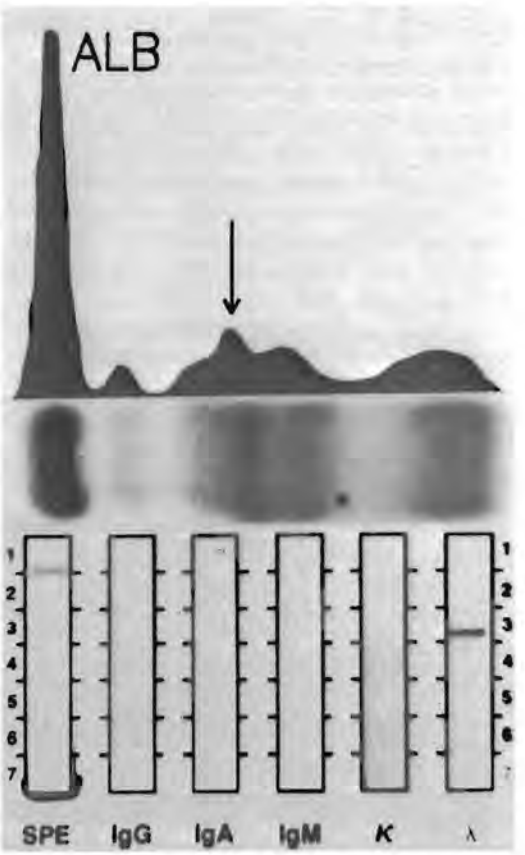

Fig. 2: Serum protein electrophoretogram and densitometric scan (top) showing an abnormal band in the inter β — α_2 region (arrow). Serum immunofixation (bottom) demonstrates the presence of λ-light chains.

overlying the tumor. The size of the lesion made satisfactory radiographs difficult, but a poorly defined osteolytic lesion with cortical expansion and destruction extending from the 33 to 47 region was identified. Teeth 44 and 45 were displaced without any sign of root resorbtion. The differential diagnoses of an ameloblastoma, osteogenic sarcoma or metastatic deposit from an unknown primary malignancy were made. The patient bled profusely from the tumor 2 weeks after admittance. Local hemostatic measures and a further whole blood infusion were needed to stabilize her condition.

Serum protein electrophoresis (SPE) showed a paraprotein band in the inter-β — α_2 area. With immunofixation (Beckman Paragon™ I.F.E., Beckman Instruments, Inc. Immuno Systems Operations Brea, C.A.) this band proved to be a monoclonal light chain of the λ-type (Fig. 2). Other stigmata of multiple myeloma included impairment of renal function, normocytic normochromic anemia and a raised erythrocyte sedimentation rate (ESR) (Table I). Unfortunately, urinalysis was not done after the provisional diagnosis of Bence Jones lambda light chain multiple myeloma had been established due to the patient's sudden exitus caused by acute renal failure.

Microscopic examination of the ante mortem biopsy of the tumor and post mortem tissue removed from the mandible and sixth rib showed extensive infiltration of immature plasma cells (plasmablasts) (Fig. 3a). There was a marked reduction of hemopoietic tissue and fat and immunoperoxidase stains (Immunolok Histoset, Immunolok Inc.; Carpinteria, USA) demonstrated the presence of λ-light chains in the cytoplasm

Table 1
THE RELEVANT BIOCHEMICAL AND HEMATOLOGICAL FINDINGS IN THE PATIENT

	PATIENT'S VALUES	REFERENCE RANGES
SERUM		
Total Protein (g/ℓ)	57	(60 - 80)
Albumin (g/ℓ)	28	(26 - 52)
Urea (mmol/ℓ)	28,9	(2,5 - 6,7)
Creatinineaμmol/ℓ)	477	(53 - 97)
IgG (g/ℓ)	9,61	(6,4 - 13,5)
IgA (g/ℓ)	1,60	(0,7 - 3,12)
IgM (g/ℓ)	0,70	(0,56 - 3,50)
HEMATOLOGY		
WBC (x10⁹/ℓ)	9,89	(7,5 ± 3,5)
RBC (x10¹²/ℓ) (Females)	2,69	(4,8 ± 0,6)
Hb (g/dℓ) (Females)	8,9	(14,0 ± 2,0)
MCV (fℓ)	90,0	(85,0 ± 8,0)
ESR (mm/h Wintrobe) (Females)	64	(0 - 20)
Platelets (x10⁹/ℓ)	338	(150 - 400)

DISCUSSION

The large, solitary expansile tumor of the mandible and absence of immunoparesis are not characteristic features of multiple myeloma. On the other hand, the age of the patient,[1,2] anemia with raised ESR,[2] absence of tooth resorbtion,[12] paresis of the jaw,[10] hemorrhagic diathesis[6] and renal complications[1] are features commonly found in patients with M.M.

Anemia is present in 80% of cases and correlates with the extent of plasma cell infiltration in the bone marrow, erythrophagocytosis by myeloma cells, folate and vitamin B_{12} deficiency or chronic blood loss due to a hemorrhagic diathesis.[2,6,13] Chronic blood loss was probably responsible for the low hemoglobin levels in our patient as erythrophagocytosis could not be demonstrated microscopically and the extent of systemic red bone marrow displacement was not sufficient to account for her anemia. Fur-

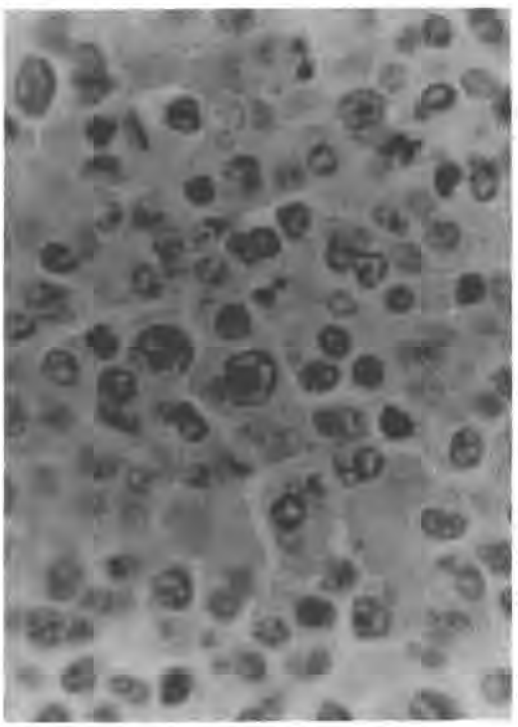

Fig. 3(a, left): Photomicrograph showing infiltration of the bone marrow by plasmablasts. (Hematoxylin and eosin stain. Magnification, x400)

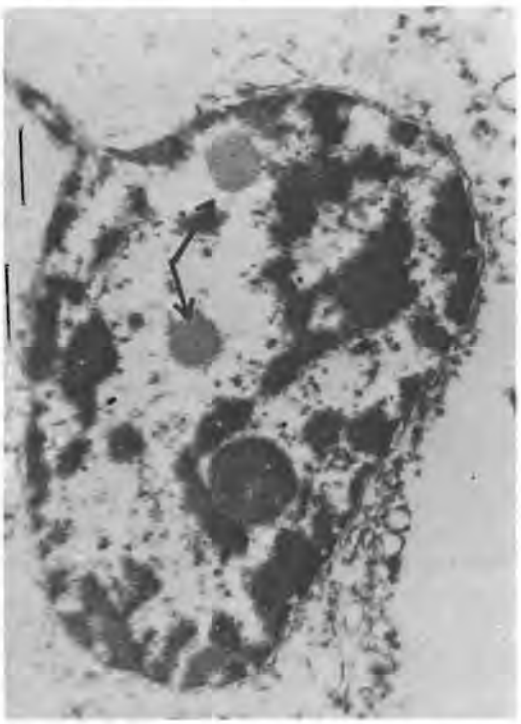

Fig. 3(b, right): Electronmicrograph of a plasmacell nucleus containing crystalline inclusions (arrows). (Magnification, x7 500.)

of the plasma cells. Congo-red stains failed to demonstrate amyloid deposits. In addition to the expected features of plasmablasts, electronmicroscopy showed intranuclear inclusions in some cells. These inclusions were not membrane bound, had a diameter of 400-700 nanometer(nm.) and a lattice-like crystalline structure. (Fig. 3b).

thermore, a megaloblastic anemia, secondary to Vitamin B_{12} or folate deficiency was absent. The mechanisms by which M.M. contribute to hemorrhagic disorders are numerous and complex. It could be the result of a thrombocytopenia secondary to the obliteration of bone marrow, interaction between myeloma proteins and coagulation factors, improper platelet function due to the "coating action" of the abnormal proteins or the hyperviscosity syndrome.[2] This syndrome has been reported in a small percentage of myelomas[14] and is the direct result of the high concentration of circulating immunoglobulin components. The increased viscosity of plasma may lead to an increased resistance to blood flow in capillaries[2] which predisposes to hemorrhages from the gingiva, mucous membranes of the gastro-intestinal tract and sites of minor surgery or trauma.[4] The bleeding tendency in our patient was not associated with a thrombocyopenia or the hyperviscosity syndrome as the platelet count and total serum protein values were normal. Impaired platelet function and interaction between coagulation factors and abnormal circulating proteins therefore seem to be the most likely cause of our patient's hemorrhagic diathesis.

A multidisciplinary approach in the diagnosis of M.M. is essential as biochemical, radiographic and microscopic parameters are not only useful in the diagnosis of suspected cases, but also provide valuable information regarding classification, stage of progression, complications and prognosis of the disease.[2,15,16]

Microscopically, a myelomatous infiltrate is classified as either plasmacytic or plasmablastic.[2] The former is characterized by small, normal appearing plasma cells with a low mitotic index and is associated with a longer survival time. The plasmablastic type shows infiltration by immature nucleolated plasma cell precursors and has a less favourable prognosis.[2,16] The diagnosis of M.M. on bone marrow plasmacytosis alone is unreliable as numerous other common conditions, like chronic inflammation, malignancies unrelated to plasma cells and autoimmune diseases often cause a plasma cell infiltrate in excess of 50 volume percent.[17,18] However, periarterial and endosteal accumulations of plasma cells, which are characteristic of M.M.,[16] were also present in our microscopic preparations. Concomitant hypoplasia of haemopoietic tissue and increased osseous remodelling are also more in favour of a neoplastic lesion rather than reactive bone marrow plasma cell infiltrate.[19] The extent of the lytic bone lesions and degree of plasmacytosis of uninvolved bone marrow adds valuable information regarding the stage of progression of disease.[16]

Immunochemical typing is helpful in predicting complications and prognoses of patients with M.M. It has been shown that light chain secreting myelomas are frequently associated with amyloidosis[4,20-23] and that they also have the highest mitotic rate.[2,24] Furthermore, the median survival time of patients with λ-light chain disease is reported to be significantly less than in κ-light chain disease.[1,24] The plasmablastic cell type and λ-light chain secretory activity placed our patient in a low prognostic category. This is supported by the rapid deterioration of her renal function which was the cause of death, a complication often encountered in patients with M.M.[25]

The absence of macroglossia and our inability to demonstrate amyloid histochemically supports Smith's observation that amyloid deposits of the tongue are not associated with M.M. of the jaws.[26] However, Smith's conclusion may be incorrect as most patients with amyloidosis present with systemic complications for which rectal, and not tongue biopsies are performed.

Detailed reports on the ultrastructure of plasma cells in M.M. have appeared in the medical[27-33] and dental[34] literature. In addition to the normal ultrastructural features of plasma cells,[28] the cells in M.M. may exhibit phagocytic vacuoles containing iron,[33] erythrocytes[20,30,33] platelets[31] and lymphocytes.[30] Perinuclear microfilaments may be responsible for cell mobility and phagocytosis.[33] Intracytoplasmic crystalline inclusions in neoplastic plasma cells have been studied extensively[28,32] and based on histochemical and ultrastructural features, these cytoplasmic inclusions are fibrillar, proteinaceous in nature and often sur-

rounded by a smooth limiting membrane.[32] Brilliant staining of the inclusions with acid phosphatase- and glucoronidase techniques suggest that they are essentially lysosomal in nature.[32] The origin of intranuclear inclusions, however, is poorly understood.[28] Absence of a membrane surrounding the intranuclear inclusions in the case under study, negates the possibility of these being located in cytoplasmic-nuclear invaginations. A transmissible agent, probably a virus, was isolated from multiple myelomas in mice,[35] mink,[36] and humans.[37] Passenger viruses, finding optimal growth conditions in the milieu of myeloma cells, have recently been reported.[29] The latticelike structure of the inclusions and the diameter of the individual crystals in our case do not resemble the shape and size of any known virus. It is therefore possible that the inclusions represents crystallization of a protein formed within the nucleus of the neoplastic plasma cells.

CONCLUSION

The presentation of the myelomatous tumour as a large, solitary expansile jaw lesion adds an interesting aspect to the reported clinical features of M.M. A multidisciplinary approach, including biochemical- and microscopical parameters is helpful in the diagnosis, prediction of complications and determination of the prognosis. Furthermore, intranuclear crystalline inclusions, as seen in this case, are probably accumulations of unknown proteins in the nuclei of the neoplastic plasmacells. This phenonemon requires further ultrastructural and biochemical investigation.

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Multiple myeloma presenting as localized expansile jaw tumour

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E. J. Raubenheimer, G. E. Lello, J. Dauth, M. S. Fayman, N. Dvornak and J. C. Senekal: Multiple myeloma presenting as localized expansile jaw tumour. Int. J. Oral Maxillofac. Surg. 1988; 17: 382–385.

Abstract. Myelomatous involvement of the maxilla is an exceptionally rare occurrence, and the presentation of the lesion as an expansile jaw bone tumour has not been reported. 2 cases, one with a maxillary lesion, the other with a mandibular lesion are presented, both of which illustrate gross bone expansions. Additionally, 1 case presented with a rare biclonal IgG kappa and IgG lambda light chain secreting myeloma. Relevant clinical, immunological, histological, biochemical and histochemical features are presented and discussed, and suggestions pertaining to surgical management made.

Key words: myeloma; jaw tumours.

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Multiple myeloma is a malignant neoplastic condition characterized by uncontrolled proliferation of a clone of abnormal plasma cells. The clinical features of the disease may be directly due to the proliferating process itself and/or indirectly to substances released by the neoplastic cells. The former results in bone marrow displacement and multiple osteolytic lesions with pathologic fractures and pain, while the latter results in the elaboration of high levels of circulating monoclonal immunoglobulins, osteoclast-activating factor and other regulating substances. The circulating monoclonal immunoglobulins or their sub-units may lead to proteinuria, renal tubular damage and amyloid deposits. Stimulation of osteoclasts may result in hypercalcaemia and bone loss.

Myelomatous infiltrates have a predilection for areas of haemopoiesis and commonly involve the calvaria and mandible[1], pelvis, ribs, sternum, clavicles and proximal portions of the humerus and femur. Multiple myeloma is usually not associated with extraskeletal lesions, but occasionally lymph nodes, liver, spleen, and other organs are involved. The preliminary clinical diagnosis often relies on the identification of multiple, punched-out, lytic bone lesions. Involvement of the maxilla is regarded as exceptional[4, 9] and the clinical presentation of myeloma as an expansile jaw bone tumour is a rarely-described feature[10]. Myeloma as an expansile bone tumour in other skeletal regions has been adequately covered in the literature. 2 cases are presented, illustrating features of expansile jaw bone tumours.

Case histories

Case no. 1

A 40-year-old black man presented with a swelling in the region of the right zygomatic eminence. The swelling had been present for a few months, and had progressively enlarged during this period. Although the patient reported some recent, unexplained weight loss, a more detailed history was unobtainable. He was a known schizophrenic for which he had received treatment for the past 3 years.

On examination, a 4 × 3 cm bony hard, painless, fixed mass was palpable in the region of the right zygomatic eminence, with softer, more nodular and slightly mobile extensions beneath the right lower eye lid, lateral to the right nasal ala, and in the right temporal region. The margins of the lesion were poorly delineated (Fig. 1a). No neck lymphnodes were palpable.

Infra-orbital nerve sensation was diminished, and intra-orally, the occlusion was unimpaired despite some expansion of the lateral wall of the sinus into the maxillary buccal vestibulum. Orbital movements were full, and gross vision intact. Although a physical examination was normal, the patient was disoriented in time and place. X-rays showed an ostcolytic lesion involving the frontal and zygomatic processes of the maxilla and the right zygoma. The antero-lateral wall of the right maxillary sinus was expanded and eroded, as was the right inferior orbital margin (Fig. 1b). A computer tomographic scan confirmed the invasion of the tumour into the inferior turbinate bone, maxillary sinus, right infratemporal space, orbital floor and palatine bone. Technetium phosphate bone scans revealed no lesions in the rest of the skeleton. A differential diagnosis of a carcinoma of the maxillary sinus, an osteogenic sarcoma or odontogenic myxoma was made at this stage. Serum protein electrophoresis showed a monoclonal band in the gamma region which on immunofixation electrophoresis (IFE) was shown to be distinct monoclonal IgG bands, one with kappa and the other with lambda light chains (Fig. 2a); IFE of urine showed low concentrations of IgG kappa only. Bradshaw and boiling tests for Bence-Jones proteinuria were negative. Immunoparesis was absent, but the patient had a slight normocytic normochromic anaemia with a severely raised erythrocyte sedimentation rate (ESR). Other relevant biochemical and haematologic findings shown in Table I were normal.

Microscopic examination of a maxillary biopsy showed a diffuse infiltrate of plasma cells. Endosteal invasion with extensive osteoclastic activity was noted (Fig. 2b) and scattered foci of tumour necrosis were associated with an infiltrate of eosinophils. Immunoperoxidase stains (Immunolok Histoset, Immunolok Inc.; Carpinteria, USA) were distinctly positive for IgG and kappa light chains and scattered neoplastic cells also reacted positively for lambda light chains, confirming the biclonal nature of the infiltrate.

A diagnosis of a biclonal IgG kappa and IgG lambda light chain-secreting myeloma with only mid-facial involvement was established and a course of radiotherapy was given.

Case no. 2

A female patient, approximately 70 years of age, was admitted from a rural hosptial with

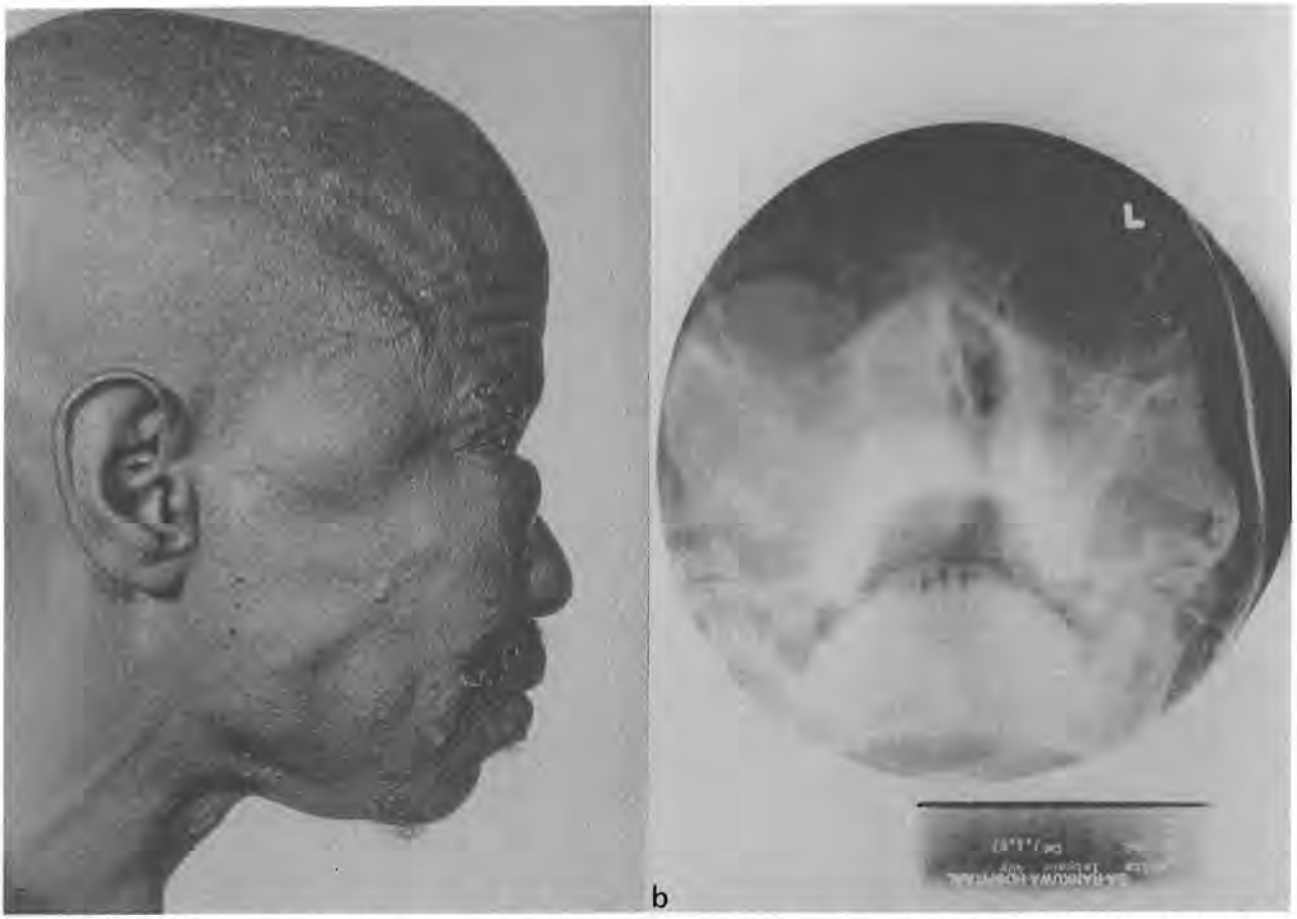

Fig. 1. (a). 40-year-old male (case no. 1) with myelomatous tumours above the right zygomatic arch, beneath the orbit, lateral to the ala and overlying the zygomatic eminence. (b) Radiograph of the case depicted in (a), showing destruction of the right maxillary sinus, inferior orbital margin, zygoma and lateral wall of the nose.

a history of painful mandibular teeth associated with a rapidly enlarging swelling. On external examination, a 10 × 6 cm tumour appeared to extend from the right mandibular second premolar area to the angle of the jaw on the left side. The tumour protruded extraorally, preventing lip closure, and sensory function of the left and right mandibular nerve was lost. Intraoral examination revealed traumatic mucosal ulcerations and severe displacement of teeth. A lipoma, 15 cm in diameter, was present in her right scapular region and she was severely anaemic. Radiographs of the mandible showed a poorly-defined lytic lesion with cortical bone destruction and extension into the symphysis of the left mandible. Full body radiographic examination revealed no further abnormalities. A clinical differential diagnosis of an odontogenic myxoma or osteogenic sarcoma was made.

Serum protein electrophoresis and immunofixation techniques showed a monoclonal lambda light chain band in the inter beta-region. Other findings included impairment of renal function, normocytic normochromic anaemia and a raised ESR (Table 1). Urinalysis was not done due to the patient's sudden exitus caused by acute renal failure. Microscopic examination of the mandibular tumour revealed a diffuse infiltrate of plasmablasts. Many cells were severely pleomorphic and extensive bone resorption was observed. All neoplastic cells stained positive with immunoperoxidase techniques for lambda light chains only. At autopsy, an interstitial nephritis with renal tubular damage, and a 1 × 2 cm lytic lesion of the right 6th rib with a microscopic appearance consistent with myeloma, was revealed. A diagnosis of lambda light-chain-secreting myeloma presenting clinically as a solitary expansible mandibular tumour, was made.

Discussion

Multiple myeloma should be distinguished from solitary plasmacytoma of bone, a condition which is described as a single plasma cell proliferation in the absence of anaemia[2]. Plasmacytoma of bone has a better prognosis than multiple myeloma and has at least a 3-year disease-free period after adequate radiotherapy. The distinction between solitary plasmacytoma and myeloma, however, is not always clear and both these disease processes probably form part of a continuous spectrum of neoplastic plasma-cell proliferation. Although our cases may have originated as plasmacytomas, we regard both as overt myelomas. Case no. 1 exhibited signs of localized dissemination with involvement of the maxilla, maxillary antrum and zygoma, and case no. 2 had a profound anaemia and a distant neoplastic deposit.

The laboratory diagnosis of multiple myeloma is multidisciplinary and primarily encompasses biochemical identification of a monoclonal peak of immunoglobulin or subunits thereof, and microscopic demonstration of a plasma cell infiltrate in excess of 30 volume % is diagnostic of myeloma[2]. Furthermore, microscopic and biochemical parameters are important in determining the prognosis of the disease. Light-chain-secreting myelomas are said to have

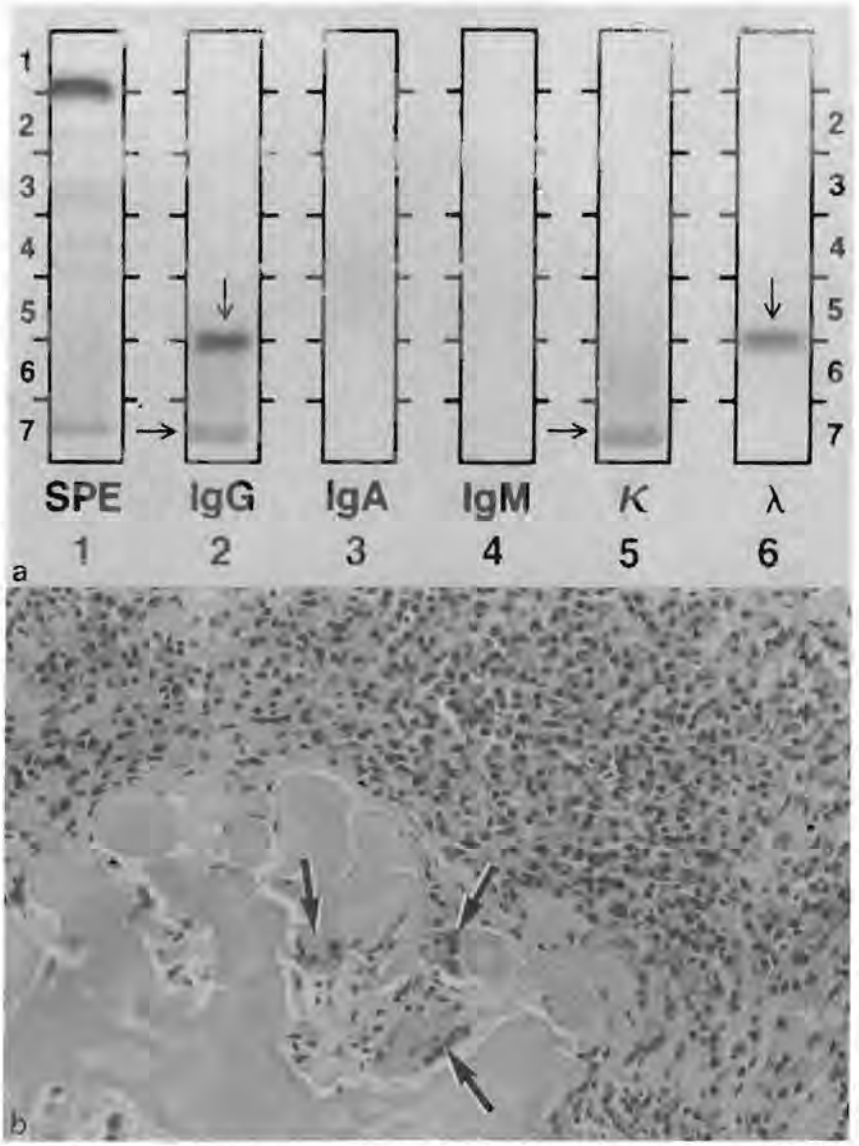

Fig. 2. (a) Serum IFE of case no. 1 showing 2 monoclonal IgG bands (arrows) with their corresponding kappa and lambda light chains (arrows). (b) Diffuse infiltrate of plasma cells (case no. 1). Note the disruption of the endosteum and osteoclastic activity (arrows). (HE stain, ×60).

the fastest growth rate and are associated with more osteolytic lesions than other immunochemical varieties[7,12] and typing of the light chain by means of IFE (or other methods), should always be carried out, because the median survival time of lambda light-chain disease is reported to be significantly shorter than kappa-light disease[5]. Plasma cell maturity and the extent of infiltration of myeloma cells in the biopsy is highly significant in predicting the duration of survival[1]. Plasmablastic myelomas are characterized by an infiltrate of nucelolated plasma cells and usually have a grave prognosis which is aggravated by hypercalcaemia and renal insufficiency[1,8].

Biclonal gammopathies, although relatively rare, are well documented[7]. These authors found 57 patients with biclonal gammopathies between 1966 and 1979 and only 6 had 2 IgG components (similar to our case no. 1). The immunoperoxidase stains of plasma cells in our case showed that there were 2 different cell populations synthesizing the para-proteins, and not a single cell population or precursor cells "switching" from one immunoglobulin class to another[6]. Furthermore, in a study of 56 patients with more than one paraprotein, Gore *et al.*[6] found no evidence that multiband myeloma has a worse prognosis than myeloma with a monoclonal protein. Kyle *et al.*[7] also found the clinical features of biclonal gammopathy and its response to therapy similar to those of monoclonal gammopathy.

Although myeloma does not present frequently as a solitary expansile tumour, it should not be excluded from the differential diagnosis of a localized expansile tumour of the jaw. If multiple myeloma is suspected, a multidisciplinary approach towards the diagnosis should always be followed. The physician should obtain a full blood count with differential and platelet counts, biochemical assessment of renal function, calcium status, serum protein electrophoresis, quantification of immunoglobulins, IFE or immunoelectrophoresis, bone marrow biopsy and aspiration, urinalysis which includes IFE and a radiographic skeleton survey[8].

Surgery has few indications in the treatment of lesions within the jaw bones. Decortication of adjacent sections of the mandible or removal of sequestrae when osteomyelitis intervenes as a consequence of impaired and depressed immunity may be necessary.

Pathological fractures of the mandible may require long-term splinting by means of arch bars or metal cap splints in order to minimize patient discomfort when fractured bone ends fail to unite. Small lesions related to pathological fractures could be excised and the gap bridged by an appropriate metal plate and fixation screws, placed well clear of the lesion, in order to splint the mobile bone segments. In this way, the patient with a good prognosis will be afforded the ability to function until such time, should it arise, when graft reconstruction may be contemplated. Immediate reconstruction of resected segments of involved bone should be attempted, particularly when a patient, debilitated only in terms of jaw function but with an otherwise good prognosis, presents for treatment. Less readily excisable lesions may be debulked, especially when encroaching upon such important organs as the eye, and particularly so when the prognosis is good. It must however be borne in mind that although a patient may present with only one detectable lesion, as in our second case, the disease is held by many to be multicentric in origin[13] and thus apparent control of the primary lesion may prove fallacious. The prognosis may be particularly difficult to determine. Furthermore, rapid deterioration and demise may occur as a result of secondary complications, as happened in our 2nd case.

Table 1. Relevant biochemical and haematological findings

	Reference ranges	Case no. 1	Case no. 2
total protein (g/l)	60–80	80	57
albumin (g/l)	26–52	33	28
urea (mmol/l)	2.5–6.7	4.4	28.9
creatinine (μmol/l)	53–97	79	477
total calcium (mmol/l)	2.25–2.70	2.25	not done
IgG (g/l)	6.4–13.5	33	9.61
IgA (g/l)	0.7–3.12	5.67	1.60
IgM (g/l)	0.56–3.50	0.66	0.70
WBC ($\times 10^9$/l)	7.5±3.5	9.17	9.89
RBC ($\times 10^{12}$/l)	4.8±0.6 (females) 5.8±1.0 (males)	4.33	2.69
Hb (g/dl)	14.0±2.0 (females) 16.4±2.8 (males)	12.6	8.9
ESR (mm/h Westergren)	3–15 (females) 1–10 (males)	104	64
platelets ($\times 10^9$/l)	150–400	355	338

These complications include predominantly renal failure, infection and anaemia. Patients presenting with multiple myeloma lesions have a poor prognosis, with a median survival time of 2–3 years, and surgical considerations should be weighed against this background and the patients' response to radiation and chemotherapy, as surgery can only be comtemplated as a palliative procedure.

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Multiple myeloma: a study of 10 cases

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The clinical, radiographical, biochemical, microscopical and ultrastructural features of 10 cases of multiple myeloma were studied. The skull and jaw regions were frequently involved by the disease and although the diagnosis remains multidisciplinary, microscopical parameters differentiating a myelomatous bone marrow infiltrate from a reactive plasmacytosis are discussed. Biochemical and microscopical factors influencing the prognosis are highlighted and significant ultrastructural findings include erythrophagocytosis, cytoplasmic nuclear asynchrony of plasmablasts and intranuclear viral like inclusions.

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Multiple myeloma (MM), a disease of the elderly, is characterized by neoplastic proliferation of a clone of plama cells capable of synthesizing and secreting immunoglobulin (Ig) or its subunits. Common systemic findings include multiple lytic bone lesions with pathologic and compression fractures, hypercalcèmia, anemia, renal tubular disease with renal insufficiency and infections secondary to immunosuppression (1). Frequent oral manifestations of multiple myeloma are pain, swelling, numbnees, mobility of teeth (2) and enlargement of the tongue, salivary glands and soft tissue tumors as a result of amyloid deposits (3). Radiolytic lesions are rarely found in the maxilla (4) and although lytic bone lesions are more frequent in the mandible, MM patients may present with diffuse osteoporosis (3), or even a destructive expansile mandibular tumor (5).

Monoclonal Ig's or fractions thereof secreted by the neoplastic plasma cells can be demonstrated in the serum and urine of the majority of patients and circulating free light chains (Bence Jones proteins) are often associated with amyloid deposits in tissues (1). Only in rare instances are the secretory products absent and these cases are referred to as non-secretory myelomas. The IgG class of MM accounts for approximately 66% while the combined IgA, IgM and Bence Jones types constitute 29% of cases. Rare variations of MM (including the IgD, IgE and heavy chain types) and biclonal and triclonal forms account for the remainder (1).

As a multitude of non-neoplastic conditions can give rise to a bone marrow plasmacytosis, the diagnosis of MM should always follow a multidisciplinary approach encompassing radiographic, biochemical and bone marrow microscopic investigations. A bone biopsy, however, provides useful information on the diagnosis, classification and staging of patients with MM (6).

A limited number of investigations on the ultrastructure of neoplastic plasma cells have been reported in the literature. Characteristically the cells exhibit large amounts of rough endoplasmic reticulum arranged in lamellar patterns, abundant mitochondria in perinuclear locations, prominent Golgi complexes (7, 8) and cytoplasmic microfilaments (9). Occasional erythrophagocytosis and uptake of cells of the myeloid series and even platelets by myeloma cells may result in a hemolytic anemia (9, 10). Intranuclear and intracytoplasmic crystalline inclusions have been suggested to be related to the process of abnormal immunoglobulin synthesis (11), may be of lysosomal origin (12) or may even represent viral inclusions (13).

This study was undertaken to correlate the light and electron microscopical appearances of biopsies of 10 consecutive cases of MM with clinical, radiographical and biochemical findings. Furthermore, the incidence of oral and skull involvement in the group of patients was determined.

Material and methods

The age and sex incidence, presenting complaints, radiographic distribution of lesions, immunochemical subtype and other relevant biochemical changes of 10 consecutive cases with MM were studied on admission. Serum total protein, albumin, urea and creatinine levels were determined with a continuous flow analyzer (SMA II, Technicon Instruments Corp, Tarrytown, NY 10591) and serum total calcium levels by atomic absorption spectrophotometry (Perkin-Elmer Corp., Norwalk, Connecticut 06856 USA). Quantitation of IgG, IgA and IgM levels were done with rate nephelometry (Auto ICS, Beckman Instruments Inc, Fullerton, USA). Immunochemical typing of the heavy and light chains in serum and concentrated urine was carried out with immunofixation electrophoresis (Paragon™ IFE gels, Beckman Instruments Inc.).

Trephine biopsies were taken of lytic bone lesions and fixed in buffered formalin and glutaraldehyde followed by osmium tetroxide for light and transmission electron microscopy respectively. Biopsies intended for light microscopy were divided into 2 portions. One portion was routinely decalcified (EDTA) and embedded in paraffin wax. Sections 4 μ thick were cut and stained with hematoxylin, eosin, Gomori's stain for reticulin fibres, periodic acid schiff (PAS) for glycoproteins, Berlin Blue stain for iron and immunoperoxidase stains (Immunolok Histo-

Table 1. Biochemical findings.

Serum	Reference value	Patient (sex and age)									
		Case 1 (M,25Y)	Case 2 (M,76Y)	Case 3 (M,72Y)	Case 4 (F,56Y)	Case 5 (F,72Y)	Case 6 (F,67Y)	Case 7 (M,65Y)	Case 8 (M,62Y)	Case 9 (M,65Y)	Case 10 (F,70Y)
Total protein (g/l)	60–80	67	63	101	97	98	61	97	140	93	57
Albumin (g/l)	28–52	38	27	24	46	29	43	31	32	31	28
Urea (mmol/l)	2.5–6.7	4.1	19.5	5.6	6.2	5.5	8.8	7.5	5.6	10.1	28.9
Creatinine (umol/l)	53–97	70	527	101	61	86	63	99	87	106	477
Total calcium (mmol/l)	2.25–2.70	1.94	2.16	2.09	not done	2.58	2.72	2.35	2.61	3.00	not done
Immunochemical type	–	Bence-Jones kappa	IgG lambda	IgG lambda	IgG kappa	IgG kappa	IgA kappa non-secretor	IgA lambda	IgG kappa	IgG kappa	Bence-Jones lambda
IgG (g/l)	6.4–13.5	12.0	15.9	84.9	37.9	65.0	6.05	8.3	104	69.9	9.6
IgA (g/l)	0.7–3.12	1.20	4.44	1.07	0.65	0.45	0.32	60.70	8.34	0.49	1.60
IgM (g/l)	0.56–3.50	0.75	1.36	0.58	0.62	0.26	0.47	0.40	0.40	0.27	0.70
Urine Light chain type		kappa	lambda	lambda	kappa	absent	absent	absent	kappa	absent	lambda

set, Immunoloc Inc., Carpinteria, California) for IgG, IgA, IgM and kappa and lambda light chains. The other portion of the biopsy was embedded in plastic without decalcification and sections 2 μ thick were cut and stained with hematoxylin, eosin, modified Gomori's stain for reticulin, methyl green pyronine stain for plasma cells and Prussian blue stain for ferric iron. Tissues for electron microscopy were embedded in Araldite and ultrathin sections were cut and examined with a Joel 100 cx II electron microscope.

Four quantitative and 3 semiquantitative parameters were studied light microscopically. The quantitative parameters included the predominant morphologic cell type (plasmablastic or plasmacytic determined by the presence or absence of a nucleolus), the immunochemical subtype (IgA, IgM, IgG, kappa or lambda), the stage of the disease (according to the quantity of plasma cell infiltration in the biopsy: Stage 1 less than 20 volume percent, Stage 2:20 – 50 vol. %, Stage 3 more than 50 vol. %) and trabecular bone volume (expressed as percentage of total surface area of the section as measured with an image analyzer). The semiquantitative parameters included the proliferation pattern of the plasma cells (nodular or diffuse), endosteal invasion, disruption of the reticulin pattern of the bone marrow and the degree of hemopoietic depression which were expressed as absent, slight, moderate or severe.

Ultrastructurally, attention was given to deviations of cytoplasmic and nuclear morphology.

Results

The series consisted of 4 female and 6 male patients and the age at diagnosis varied from 25–76 years (mean 63 years). Two patients presented with complaints of generalized skeletal pains, 2 with vertebral collapse and paraplegia, 2 with oral and paraoral complications and one with a pathological fracture of the left femur. The presenting symptoms of 3 patients were unknown. Of the 3 with oral complaints, Case 1 had an enlarged tongue, parotid glands and mucosal swellings. Microscopical examination of these lesions revealed extensive amyloid deposits. The other, Case 10, had a large tumour (10×6 cm) consisting of a neoplastic plasma cell infiltrate involving the anterior mandible.

Table 2. Microscopical findings.

Microscopical parameter	Patients									
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Morphological cell type	Plasma-cytic	Plasma-blastic	Plasma-blastic	Plasma-cytic	Plasma-cytic	Plasma-cytic	Plasma-blastic	Plasma-cytic	Plasma-cytic	Plasma-blastic with bizarre cells
Immunochemical cell type	kappa	IgG lambda	IgG lambda	IgG kappa	IgG kappa	IgA kappa	IgA lambda	IgG kappa	negative	negative
Stage	3	3	3	3	2	1	2	3	2	3
Trabecular bone volume	8.31	0.52	13.52	21.03	0.12	13.68	16.21	11	10.14	18
Proliferation pattern	diffuse	nodular	diffuse	diffuse	diffuse	diffuse	diffuse	diffuse	nodular	nodular
Endosteal invasion	absent	present	present	present	absent	absent	present	present	absent	present
Reticulin disruption	+++	++	++	++	+	–	+	+++	+	+++
Hemopoietic depression	+++	++	+++	++	+	–	–	+++	–	+++

– = absent
+ = slight
++ = moderate
+++ = severe

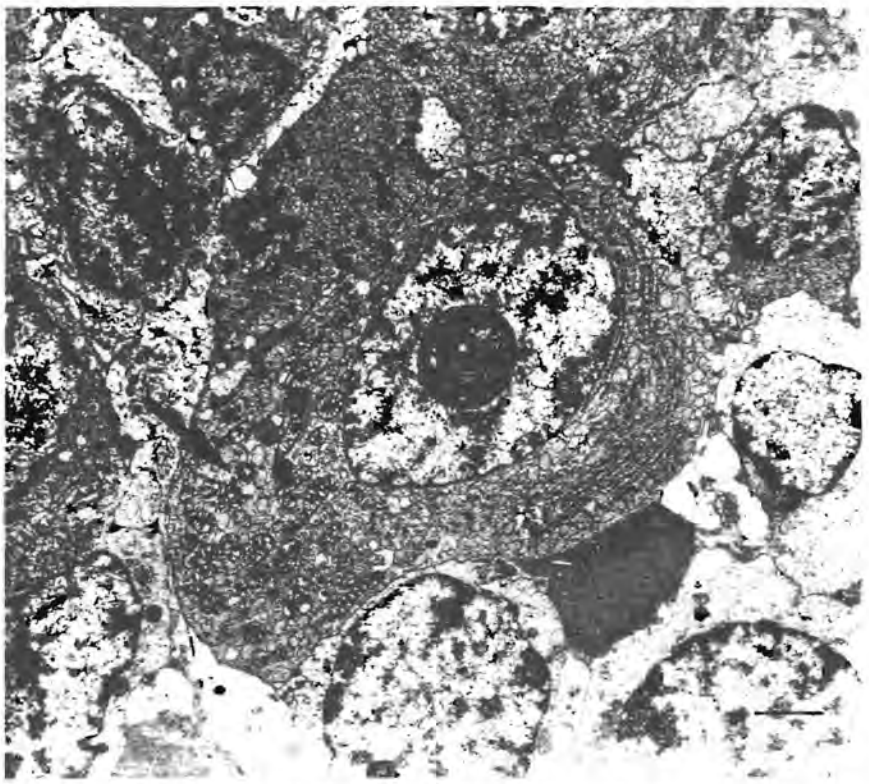

Fig. 1. Electron micrograph of a plasmablast. Note the prominent nucleolus and mature cytoplasm with endoplasmic reticulum, mitochondria and lysosomal iron pigment (arrow) (Bar = 2μ).

Multiple radiolytic lesions were present in 5 patients and involved the skull and vertebral bodies (4 cases), pelvic bones (3 cases) ribs and long bones (2 cases) and mandible (1 case). Localized lesions were present in 2 patients, affecting the femur head (Case 9) and mandible (Case 10). Case 6 exhibited diffuse osteoporosis, while one case had no bone lesions (Case 3) and radiographs were unobtainable in Case 2. Post mortem examination of the patient with the expansile mandibular tumor (Case 10) revealed an additional myelomatous deposit in the right sixth rib.

The relevant biochemical findings are shown in Table 1. The most common immunochemical type of MM was IgG kappa followed by IgG lambda. Light chains were absent from urine in 4 cases, one being the IgA non-secretor myeloma. Suppression of the levels of one or more normal (residual) immunoglobulins was found in 6 cases. Three cases had hypocalcemia and severe hypercalcemia was present in one case only (Case 9).

The microscopical findings are reflected in Table 2. Four cases were of the plasmablastic type (Fig. 1) and 6 cases of the plasmacytic type. Gomori stains were particularly helpful in identifying disruption of the reticulin fibre system of the bone marrow and the pattern of proliferation. Endosteal invasion with increased osteoclastic activity was identified in 6 cases (Fig. 2). Of all myelomas, those with multiple lytic lesions exhibited the least bone (9.86% of the total surface area of the section compared to an average 14.07% for cases with one or no lytic lesions). The one case with diffuse osteoporosis and no lytic lesions (Case 5) only had as little as 0.12% trabecular bone in the biopsy. Abundant cytoplasmic colloid, reacting with the PAS technique, was a prominent feature of the neoplastic cells in Case 6 (the non-secretor myeloma) and the immunoperoxidase technique confirmed the presence of intracytoplasmic IgA and kappa light chains in these cells. Immunoperoxidase stains facilitated the identification of the monoclonal nature of the infiltrate and correlated positively with the immunochemical type in 8 cases, the remaining 2 (Cases 9, 10) being negative with this technique.

In contrast to the ultrastructural features of normal plasma cells, electron microscopical investigations revealed a distended endoplasmic reticulum containing colloid in Case 6 (Fig. 3), red blood cell phagocytosis and lysosomal iron pigment in Cases 4 and 8 (Fig. 1), prominent cytoplasmic microfilaments in Cases 3 and 8, and cytoplasmic constrictions suggesting amoeboid movement and numerous microvilli on cell surfaces adjacent to other plasmacells

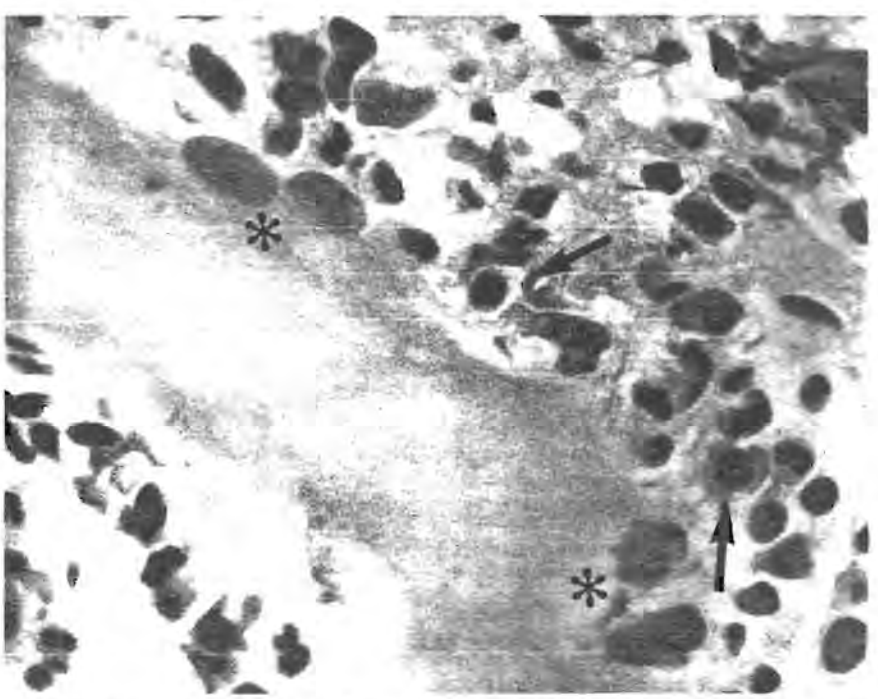

Fig. 2. Photomicrogaph showing endosteal invasion by neoplastic plasma cells (arrows) with osteoclastic activation (asterisk) and bone resorption (H&E, ×400).

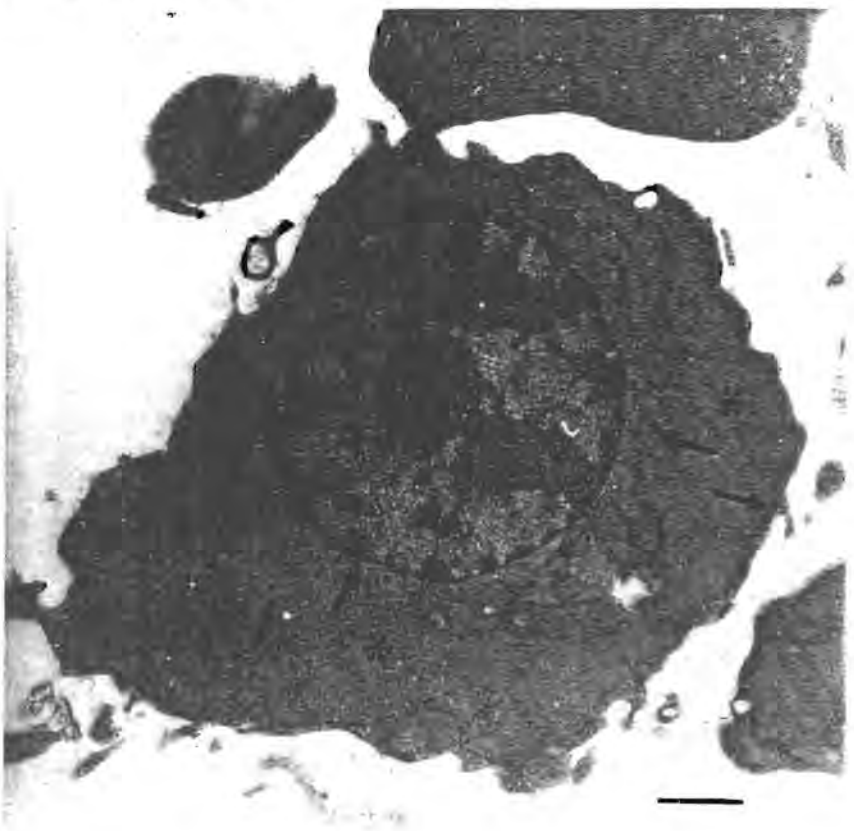

Fig. 3. Electron micrograph of a plasma cell in Case 6 showing distended endoplasmic reticulum (arrows) containing colloid (asterisk) (Bar = 2μ).

in Case 8 (Fig. 4). Case 10 showed intranuclear lattice like crystalline inclusions (Fig. 5) and all plasmablastic myelomas exhibited a discrepancy between nuclear and cytyoplamic maturity (Fig. 1).

Three patients (Cases 1, 5 and 10) died within one year of diagnosis. Post mortem examination revealed a chronic interstitial nephritis with renal tubular damage in Cases 1 and 10 and a fulminant opportunistic lung infection in Case 5.

Discussion

The average age at the time of diagnosis of multiple myeloma is reported to be 62 years with less than 2% of all cases occuring before 40 years (14). These findings are supported by our series except for Case 1 whom should be regarded as exceptionally young for MM.

Involvement of the paraoral tissues, jaw and cranium ranks high as presenting clinical features of multiple myeloma. In a radiographic and case record survey of 59 cases, Bruce and Royer (4) found jaw involvement in 17 patients with MM. A more recent study indicated that the incidence of jaw involvement may even be higher (16). In our series 3 patients had radiographic demonstrable jaw lesions: one had a lytic lesion of the mandibular ramus (as part of multiple skeletal radiolucencies), one presented with a mandibular tumor which proved to be a myelomatous infiltrate and one patient presented with mandibular osteoporosis as part of a generalized osteoporosis. Furthermore, extensive oral and paraoral amyloid deposits in a fourth patient caused us to suspect and to investigate for MM, proving that oral involvement in this disease may be as high as 40%. If cranial involvement is also taken into account, the skull and jaw may be regarded as the region most commonly affected by MM. The extent of hemopoiesis in the calvaria of the skull may serve to explain this phenomenon as myelomatous infiltrates are reported to have a predilection for these areas (2, 4). The low incidence of maxillary involvement in MM (17) is supported by our study.

The occurence of the different immunochemical subtypes of myeloma in our study follows the pattern reported in the literature (1). However, Case 6, being a non-secretory IgA MM did not show any detectable paraprotein in the serum or urine. The final diagnosis was established only after radiographic and microscopic bone marrow investigations with immunoperoxidase staining had been performed. The presence of immune suppression further supported the diagnosis of MM. Non-secretory MM is a rare condition with a reported incidence of 1–5% of cases of MM (18, 19). Although our study indicates that immune suppression with decreased levels of one or more residual immunoglobulins do not occur in as many as the reported 98% of myeloma patients (1),

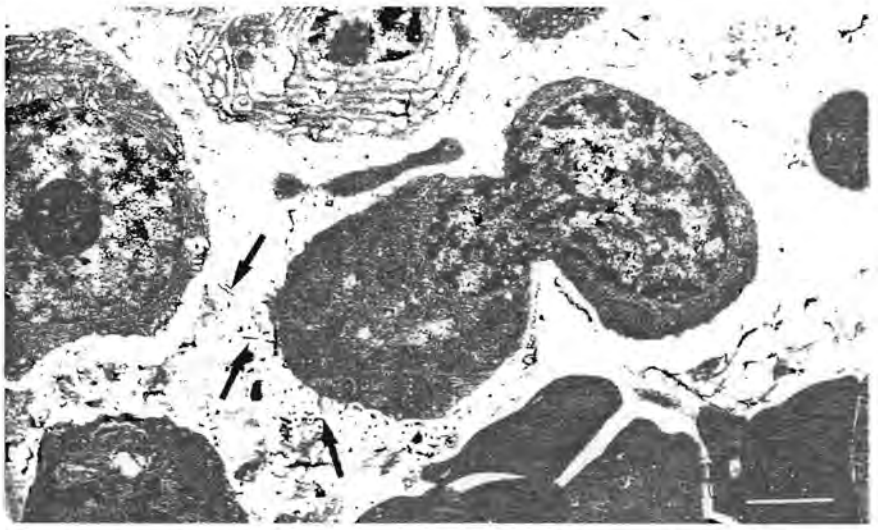

Fig. 4. Electron micrograph of plasma cell with a cytoplasmic constriction (centre). Note microvilli on the opposed surfaces of adjacent plasma cells (arrows) (Bar = 4μ).

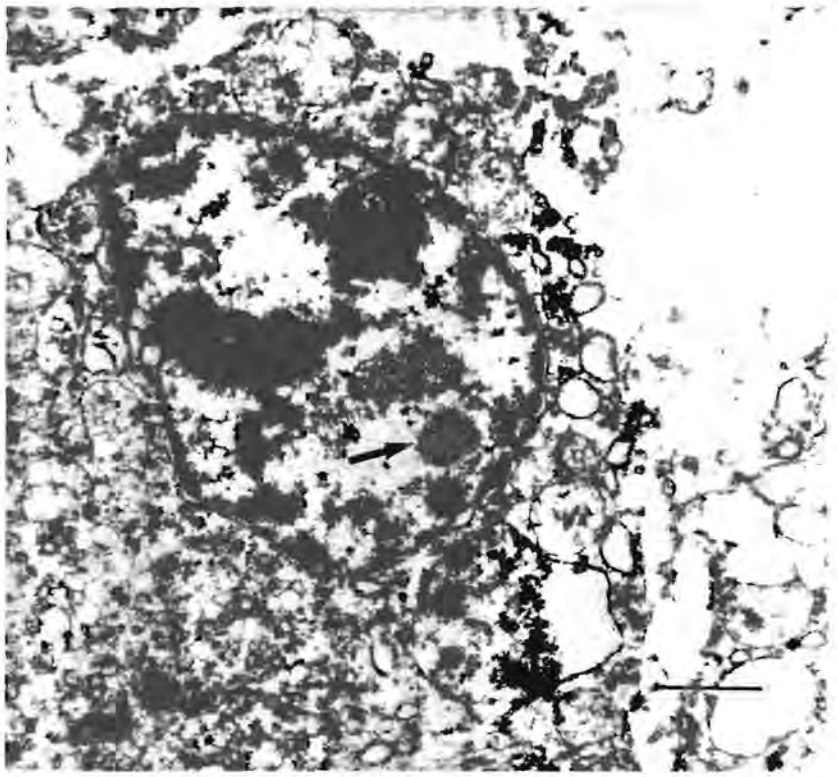

Fig. 5. Electron micrograph of tissue removed during autopsy from Case 6. The nucleus of a plasmablast contains a proteinaceous viral-like inclusion (arrow) and the cytoplasm shows autolytic change (Bar = 2μ).

this complication, which was identified in 6 of our cases, may lead to opportunistic infections and death.

Renal involvement due to the excretion of excessive light chains (20) and hypercalcemia (14) are 2 of the most important causes of renal failure and death in patients with myeloma. Light chain secreting myelomas are said to have the fastest growth rate and is associated with more osteolytic lesions than other immunochemical varieties (21). Furthermore, the median survival time of lambda-light chain disease is reported to be significantly shorter than kappa light chain disease (15, 21). Although our series was not large enough to draw definite conclusions on the prognosis of the immunochemical subtypes, both patients with light chain disease died within one year of diagnosis.

Neoplastic plasmacells are capable of inducing bone resorption by secreting osteoclast activating factor (OAF) (22), a phenomenon which is reported to be associated with frequent hypercalcemia (1, 23). Although our study supports the occurence of increased osteoclastic activity and bone loss in MM, a low to normal level of total circulating calcium appear to be more prevelant than hypercalcemia. As approximately one half of the total calcium is bound to albumin (25), hypocalcemia in patients with multiple myeloma may be associated with low levels of albumin which may be secondary to renal damage with albuminuria. However, only Case 2 with hypocalcemia had severe renal function impairment with low albumin levels while Case 1 with the lowest total calcium concentration had a normal serum albumin level. The reason for these findings remain unclear but we feel that the determination of ionized calcium levels in cases with MM may be more helpful as these determinations give a better assessment of the calcemic status especially in patients with renal function impairment (25).

Although microscopical examination of a bone marrow biopsy is reported to be more reliable in the diagnosis of multiple myeloma than aspiration cytology (6), the former technique has its limitations. It is often difficult to distinguish a neoplastic from a reactive bone marrow infiltrate, as the latter could lead to a bone marrow plasmacytosis in excess of 50 volume percent (26). Our study supports the observations of Bartl et al. (6) that microscopic findings such as the monoclonal nature of the infiltrate, plasma cell maturity, endosteal invasion, depression of hemopoiesis, bone resorption and disruption of the reticulin fibre pattern may be helpful in identifying a myematous infiltrate in a bone marrow biopsy. Furthermore, Stage 3 infiltrates in our patients were associated with moderate to severe reticulin fibre disruption and hemopoietic depression and exhibited more frequent endosteal invasion than Stages 1 and 2. With progression of the disease, the significance of the abovementioned microscopic parameters therefore appears to increase. It should be emphasized however, that unless the microscopical changes are convincing, the diagnosis of MM should not be established without biochemical and radiographic support.

Multiple myeloma of the plasmacytic type is characterized by the infiltration of small normal appearing plasma cells. The infiltrate in plasmablastic myelomas, on the other hand, are characterized by nucleolated and often pleomorphic cells. The higher mitotic rate of plasmablasts compared to plasmacytes and the fact that 2 of the 4 patients in our series with plasmablastic myelomas died within one year of diagnosis, support's Bartl's observation (6) that this type is associated with a rapid clinical deterioration.

Ultrastructurally, all plasmablastic infiltrates had a primitive nucleolated nucleus contained in a highly differentiated organelle-rich cytoplasm. The discrepancy in nuclear/cytoplasmic maturity (or nuclear/cytoplasmic asynchrony) may prove helpful in distinguishing neoplastic from reactive plasmablasts, the latter which would be expected to show matching cytoplasmic maturity with nuclear morphology. Cytoplasmic microfilaments may facilitate amoeboid movement and the identification of erythrophagocytosis may serve to explain the occurance of anemia, especially in cases not associated with extensive neoplastic bone marrow displacement. The significance of cytoplasmic microvilli which appeared to make contact with adjacent neoplastic cells remains speculative. Distention of the rough endoplasmic reticulum in the non-secretor myeloma cells may be indicative of an intact synthetic but defective immunoglobulin excretory mechanism. Immunoperoxidase stains support this observation as monoclonal cytoplasmic immunoglobulins of the IgA kappa type could be identified in this case. The lattice-like intranuclear inclusions identified in Case 10 were

not membrane bound and, therefore, do not represent nuclear invagination of crystalline cytoplasmic proteinaceous deposits. The inclusions may either be related to intranuclear protein synthesis (11) or represent 'passenger' virusses (13) finding optimal growth conditions within the milieu of the myeloma cell.

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Histopathology 1991, **19**, 380–382

BRIEF REPORT

Non-secretory IgA κ myeloma with distended endoplasmic reticulum: a case report

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A case of non-secretory multiple myeloma is presented. Plasma cells showed abundant cytoplasmic colloid contained in distended rough endoplasmic reticulum. Uniform cytoplasmic positivity for IgA heavy- and κ light-chains was demonstrated with the immunoperoxidase staining technique. It is proposed that distension of the endoplasmic reticulum by immunoglobulin-related proteins is indicative of a block in their excretion or of the presence of active synthesis of the immunoglobulins or their subunits.

Keywords: non-secretory myeloma, ultrastructure

Introduction

Non-secretory myelomas comprise approximately 1% of cases with multiple myeloma[1]. The laboratory diagnosis of this condition is made difficult by the absence of circulating monoclonal protein, and pathologists have to rely on the clinical presentation, radiographs and microscopic findings for the diagnosis and subsequent typing of the infiltrate.

Case report

A 57-year-old woman presented with generalized bone pains, weight loss and a pathological fracture of the left femur. Radiographic studies showed diffuse osteolytic bone lesions highly suggestive of multiple myeloma. Neither specimens submitted for serum and urine protein electrophoreses nor those submitted for immuno-fixation electrophoreses showed any monoclonal proteins. Other significant biochemical changes were paresis of IgG, IgA and IgM and hypercalcaemia. The erythrocyte sedimentation rate was elevated and the patient had a normocytic, normochromic anaemia.

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PATHOLOGICAL FINDINGS

A bone marrow aspiration and needle biopsy showed a diffuse infiltrate of plasma cells in excess of 30% of the total cell count. Most of the plasma cells contained abundant cytoplasmic colloid displacing the nucleus (Figure 1a). Immunoperoxidase staining of bone marrow sections showed the uniform presence of IgA heavy- and κ light-chains in the distended cytoplasm of the plasma cells (Figure 1). Stains for other immunoglobulin heavy and light chains were negative. Electronmicroscopical studies of the plasma cells showed distended endoplasmic reticulum containing colloid (Figure 1b).

On account of the monoclonal plasma cell infiltrate, the clinical, biochemical, haematological and radiographic appearances and an absence of a circulating monoclonal component, the diagnosis of a non-secreting IgA κ myeloma was made.

Discussion

Failure to detect a monoclonal component in the serum and/or urine of a patient with other clinical signs of myeloma is the characteristic feature of non-secretory myeloma. Significant abnormalities found in our patient and supporting the diagnosis of myeloma were multiple lytic bone lesions, immunoparesis, a raised serum calcium, elevated erythrocyte sedimentation rate, anaemia and a bone marrow plasmacytosis in excess of 30%. Immunoperoxidase stains proved the infiltrate of plasma cells to be a monoclonal IgA κ type.

The term non-secretory, coined for this variety of

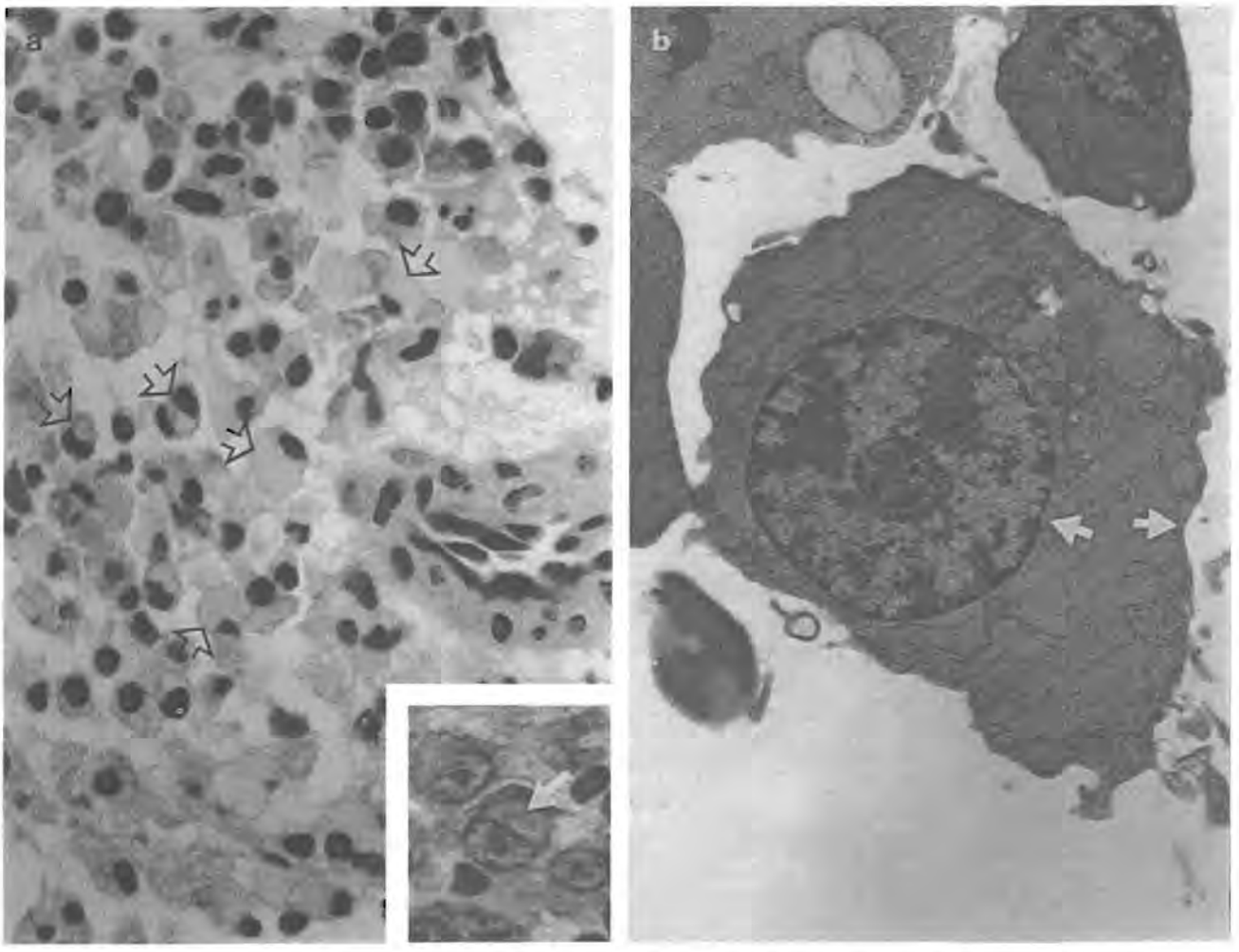

Figure 1. a Light microscopy of a bone marrow section, showing plasma cells with abundant cytoplasmic colloid (arrows). *Inset*: positive staining of the cytoplasmic colloid for IgA. **b** Electronmicroscopical view of a plasma cell with distended endoplasmic reticulum (arrows). ×8200.

myeloma, implies that a block in its release rather than in its synthesis accounts for the absence of a paraproteinaemia. The absence of a circulating monoclonal spike associated with the lack of intracellular immunoglobulins, on the other hand, suggests a block in immunoglobulin production[2]. These cases are often referred to as 'non-producers'[3] and immunoperoxidase stains for immunoglobulin typing would be negative.

The phenomenon of non-secretion in multiple myeloma is perplexing. Most studies have failed to reveal plasma cell abnormalities associated with the lack of a circulating monoclonal protein in non-secretory myelomas[2,4]. It is accepted, however, that the degree of distension of the rough endoplasmic reticulum cisternae in plasma cells at any particular time is influenced by the amount of immunoglobulin synthesized and the kinetics of its secretion. The distension of the rough endoplasmic reticulum by immunoglobulin-related proteins in our patient is, therefore, indicative of a block in excretion in the presence of active synthesis of the immunoglobulins or their subunits. It is important to note that plasma cells with distended endoplasmic reticulum are occasionally observed in infiltrates of secretory types of multiple myeloma[5]. It would be interesting to determine whether these cells also exhibit decreased secretory activity.

The signet-ring cell change exhibited by the IgG κ myeloma reported by Eyden & Banerjee[6] resembles the infiltrate in our case and was also caused by large cytoplasmic membrane bound vesicles which compressed the nucleus against the cell membrane. Although the authors postulate the phenomenon to represent a membrane re-cycling defect, strong vacuolar staining for IgG and κ light-chains is indicative of a process similar to that proposed in our case.

Acknowledgements

We are indebted to Mrs C.S.Begemann for secretarial assistance and Mr H.Ebrahim for photographic services.

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BRIEF REPORT

So-called cutaneous lymphadenoma: a lymphotropic solid syringoma?

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Keywords: cutaneous lymphadenoma, syringoma, skin neoplasm

Introduction

Lymphadenoma is a newly characterized skin neoplasm, occurring mostly in the head and neck region of young and middle-aged adults[1]. The histogenesis of this peculiar tumour is unknown, but it has been suggested to be of possible pilosebaceous derivation. We report one such case, and provide evidence that this represents a sweat duct tumour.

Case report

A 30-year-old woman presented with a skin nodule over the left upper eyelid. A whitish firm nodule measuring $6 \times 5 \times 3$ mm was excised with the overlying ellipse of skin. There was no recurrence after 2 years.

The lesion was located in the dermis and was non-circumscribed (Figure 1). It was composed of irregular, sometimes anastomosing, epithelial islands of variable sizes and shapes dispersed among a cellular fibrous stroma. Some of the islands assumed a tadpole-shaped configuration. These islands were bounded by one to several layers of vaguely palisaded epithelial cells. Their centres were composed of more loosely arranged cells, including some large polygonal cells with retracted eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli, reminiscent of lacunar cells (Figure 2). There was a variable infiltrate of small lymphocytes possessing slightly irregular or elongated nuclei. Rarely, ductules lined by a single layer of cuboidal cells were found within the epithelial islands (Figure 3a). They were highlighted by immunostaining for carcino-embryonic antigen (Figure 3b), which also stained the surrounding sweat ducts and sebaceous glands. The epithelial nature of the cellular islands, including the large cells, was confirmed by immunostaining for cytokeratin (AE1/AE3, CAM 5.2). Staining with CAM 5.2 was generally weak, whereas staining with AE1/AE3 was more intense, with accentuation in the ductular elements within the epithelial islands. The cellular islands showed weak cytoplasmic staining for epithelial membrane antigen, while the ductules showed strong luminal staining. Immuno-

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Multiple myeloma and amyloidosis of the tongue

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Raubenheimer EJ, Dauth J, Pretorius FJ. Multiple myeloma and amyloidosis of the tongue. J Oral Pathol 1988: 17: 554–559.

Tongue biopsies of 30 diagnosed cases of multiple myeloma were examined light and electron microscopically and amyloid deposits were identified in 8 patients. Immunochemical typing of amyloid in kappa and lambda subtypes was performed successfully although positive staining of tissue-associated immunoglobulin light chains made reliable identification of amyloid with this technique difficult. Cells of macrophage lineage appear to play a central role in light chain-associated amyloidogenesis. Our findings do not agree with the reported higher amyloidogenic potential of lambda light chains and we were unable to show a positive correlation between the percentage plasma cells in bone marrow aspirates or the presence of urinary light chains and myeloma-associated amyloidosis.

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Multiple myeloma (MM) is characterized by a malignant proliferation of plasma cells which, in most instances, secrete large quantities of monoclonal immunoglobulins or subunits thereof. Amyloidosis is frequent in patients suffering from MM and leads to organ dysfunction including cardiac and renal failure, malabsorption syndromes, and peripheral neuropathies (1). It is generally agreed that amyloid fibrils in patients with MM are derived from monoclonal immunoglobulin light chains (Bence Jones proteins) (2). Although the exact mechanism involved in the extracellular depositioned of light chain-associated amyloid is less clear, considerable evidence supports the role

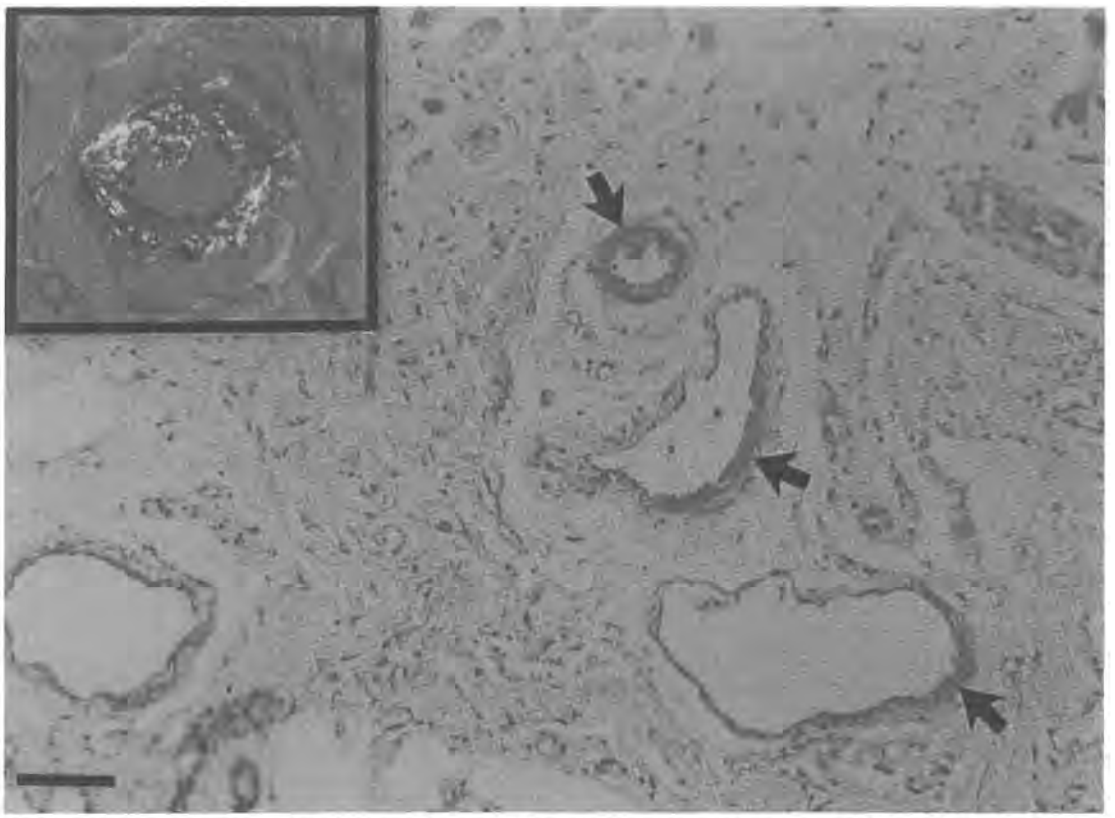

Fig. 1a. Mild perivascular amyloid deposits (arrows) in Case 7. (Congo red stain, bar = 50 μ) Inset: Congo red stain viewed with polarized light.

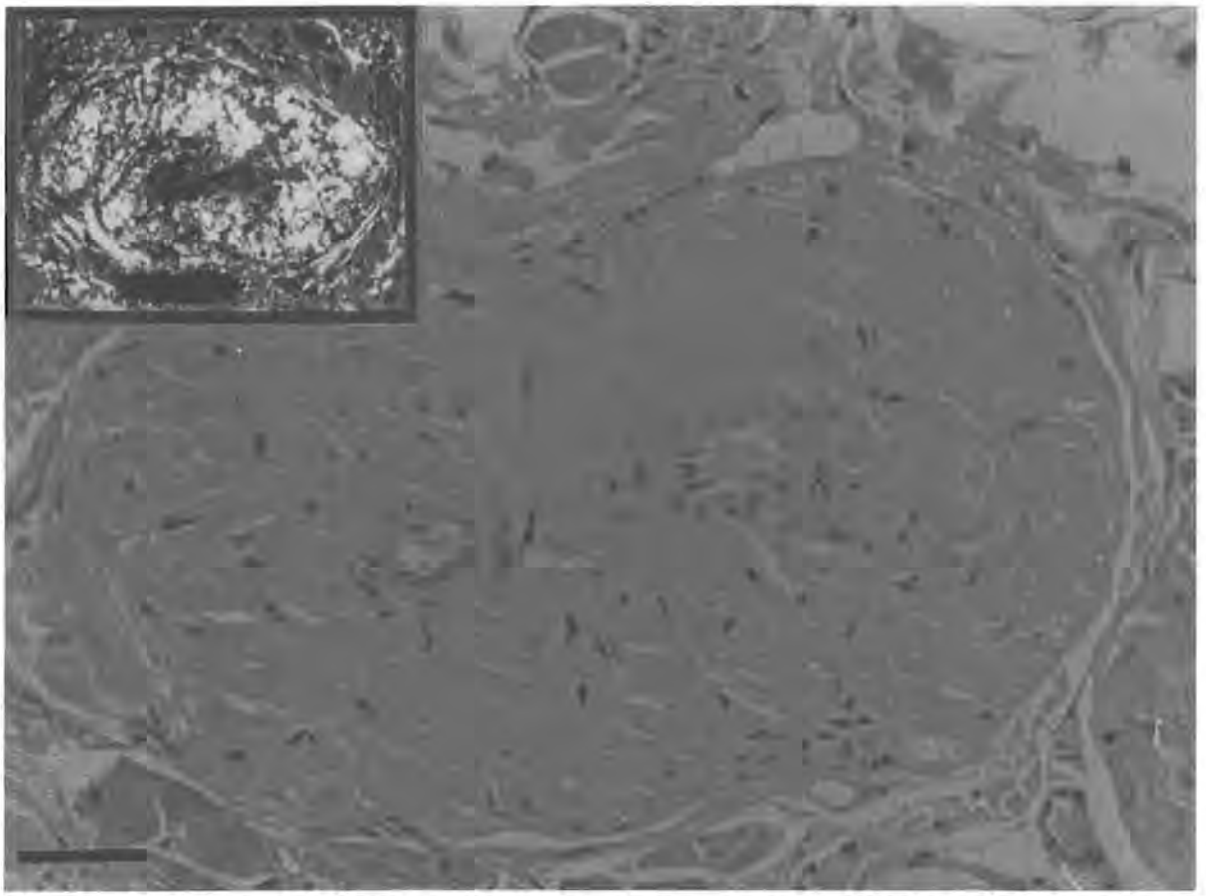

Fig. 1b. Severe perivascular amyloid deposits in Case 1. (Congo red stain, bar = 35 μ) Inset: Congo red stain viewed with polarized light.

macrophages play in MM-related amyloidogenesis (3). The light chain class found in amyloidosis in MM is reported to be more commonly of the lambda than the kappa type with a frequency of 2 to 1. This ratio is the reverse of that seen in most cases of monoclonal gammopathy (1). Furthermore, amyloidogenesis in MM appears to be related to the presence of kappa or lambda light chains in urine and a high percentage bone marrow plasma cells (4).

It was previously stressed that primary amyloidosis (including amyloidosis occurring with MM) typically involves such mesodermal tissues as smooth and skeletal muscle, as well as the cardiovascular system, whereas secondary amyloidosis affects the liver, spleen and kidneys (5). An extensive overlap in the distribution of primary and secondary amyloidosis has been reported (6, 7) and differential organ involvement is no longer considered to be a useful basis for the classification of amyloidosis. With increasing acceptance of the role light chains play in amyloidogenesis, the amyloid type associated with MM was designated AL protein (A for amyloid fibril protein and L for immunoglobulin light chain) in recent amyloid classification systems (1).

The purpose of this study was to determine the incidence of amyloidosis of the tongue in patients with MM admitted to the Ga-Rankuwa hospital. Furthermore, immunochemical subtyping of amyloid deposits was performed and the biochemical changes associated with MM-related amyloid deposits noted.

Material and methods

The tongues of 30 proven cases of MM were examined clinically and incision biopsies were performed on the lateral borders thereof. The tissue was divided and fixed in 3% buffered formalin and 4% glutaraldehyde and processed for LM and TEM, respectively. Sections for LM were stained with H&E, Congo red stain for amyloid and the immunoperoxidase technique (Immunolok Histoset, Immunolok, Carpinteria, CA) was employed for the detection of kappa and lambda light chains and IgG, IgA, or IgM. Heavy and light chains in the serum and urine were typed utilizing immunofixation electrophoresis (Paragon ™ IFE Gels, Beckman Instruments, Fullerton, U.S.A.) and immunoglobulin concentrations, as well as light chain levels in the serum and urine, were quantitated by rate nephelometry (Auto ICS, Beckman). Bone marrow aspirations of the iliac crest or sternum were performed as part of the diagnosis of MM and the volume of plasma cells expressed as a percentage of the total nucleate cell count. The microscopic features were correlated with the percentage plasma cells in the bone marrow aspirates, the secretory type of myeloma and serum and urinary biochemical findings.

Results

Biopsy wounds of all cases healed without complication or patient complaints except in Case 26 where an unexpected hemorrhage occurred. This complication was, however, readily brought under control by suturing.

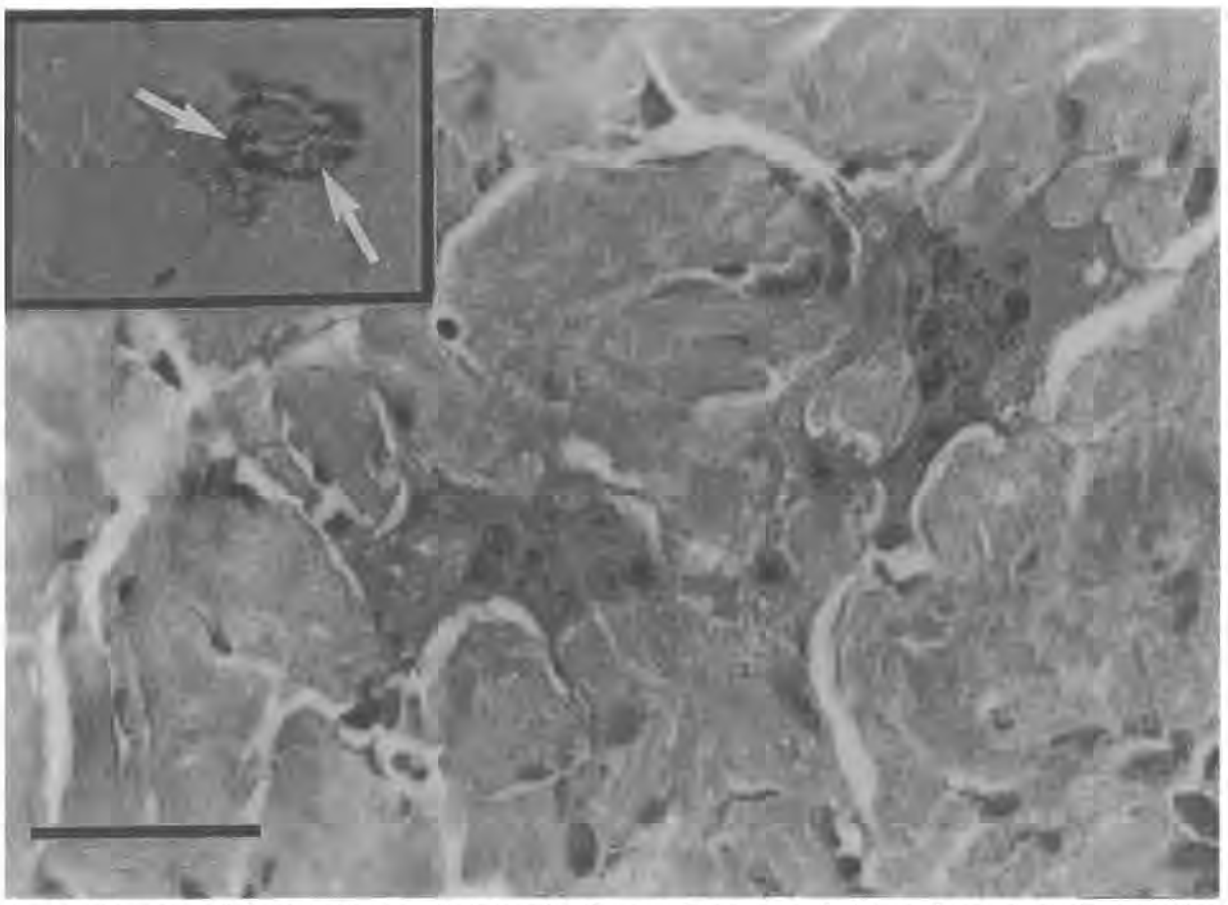

Fig. 1c. Diffuse amyloid deposits with giant cells in Case 17. (Congo red stain, bar = 40 μ) Inset: Giant cell containing cytoplasmic kappa chains (arrows) (Immunoperoxidase stain for kappa light chains).

Examination of Congo red stains viewed with polarized light identified amyloid deposits in 7 cases, ranging from mild (4 cases, Fig. 1a) to severe (1 case, Fig. 1b) perivascular deposits. Two cases exhibited diffuse amyloid deposits extending against an atrophic mucous membrane. The amyloid in the latter patients contained large, dilated and thin walled bloodvessels and many macrophages and giant cells (Fig. 1c). Of the positive cases, only 3 exhibited macroglossia, 2 of which had mucosal atrophy, diffuse amyloid deposits and mucosal nodules composed of amyloid. Tongue enlargement was present in 4 patients without amyloidosis (Table 1).

Electron microscopic examination confirmed amyloid in all positive cases and identified in addition, amyloid fibrils in an eighth patient (Fig. 1d).Immunoperoxidase stains for light chains showed kappa or lambda positivity of amyloid which corresponded to the relevant MM light chain type in the serum. Positive staining of tissue associated-monoclonal immunoglobulins and light chains concurring with the MM secretory type, made identification of small amyloid deposits in the immunoperoxidase stained sections difficult (Fig. 2). The relevant MM light chain was present in the cytoplasm of amyloid-associated giant cells in the 2 cases with diffuse mucosal deposits (Fig. 1c). Immunoperoxidase stains further identified in both amyloid-positive and -negative cases the relevant monoclonal immunoglobulin and light chain type in groups of keratinocytes and spindleshaped cells in the basal cell region of the mucous membrane (Fig. 3). The positive epithelial cells corresponded to foci of clear cells observed in hematoxylin- and eosin-stained sections.

Four patients, 2 of whom had amyloid deposits, were under 35 years old, well below the reported mean age of 62 years for MM (8). Case 13, who presented with a solitary maxillary tumor, had a biclonal gammopathy (IgG kappa and IgG lambda). Urinary light chains were absent in 3 cases with amyloidosis. One patient with amyloidosis (Case 13) only had 10% plasma cells in his bone marrow aspirate. Other relevant clinical, biochemical and microscopical findings are in Table 1.

Discussion

To date there is no accurate non-invasive diagnostic procedure for amyloidosis. Although rectal biopsies have been advocated as more successful than biopsies of the gingiva for the identification of amyloid (9), the risks and patient discomfort are greater than with intraoral biopsy techniques (10). Despite immune suppression which occurs frequently in patients with MM, post biopsy infections were not encountered in our study. The difficulty in controlling hemorrhage and the high risk of infection following rectal biopsy render this procedure less attractive. As amyloid deposits are often limited to the deeper parts of the submucosa (1), tongue biopsies are more appropriate than the more superficial gingival biopsies. This study furthermore indicates that tongue biopsies are probably more

Table 1. Clinical, biochemical, and microscopical data of 30 MM patients.

Case no	Age	Sex	MM type	Tongue enlargement	Residual Ig levels	Urinary		% plasma cells	Amyloid	
						light K	chain λ		type	distribution
1	66	F	Gκ	Yes	↓	−	−	60	K	Severe pv.
2	34	M	Gλ	No	↓	−	+	65	λ	Mild pv.
3	60	F	Gλ	No	↓	−	−	5	−	−
4	69	M	Aκ	Yes	↓	−	−	70	−	−
5	78	M	Gκ	No	Normal	+	−	30	−	−
6	79	M	Gκ	No	↓	−	−	80	−	−
7	60	F	Gκ	No	↓	+	−	40	K	Mild pv.
8	60	M	Aκ	No	↓	+	−	30	K	Mild pv.
9	42	M	Gλ	Yes	↓	−	+	80	−	−
10	72	M	Gλ	No	Normal	−	−	5	−	−
11	36	M	Gκ	No	Normal	−	−	3	−	−
12	52	M	Gκ		↓	+	−	30	−	−
13	40	M	Gκ+Gλ	No	Normal	−	−	10	N.A.	EM pv.
14	45	M	Aκ	No	↓	+	−	15	−	−
15	40	F	Aλ	No	↓	−	+	30	−	−
16	60	F	Aλ	No	↓	−	+	N.A.	−	−
17	25	M	κ	Yes	Normal	+	−	30	K	Diffuse
18	70	F	λ	No	Normal	N.A.	N.A.	N.A.	−	−
19	57	M	Gλ	Yes	Normal	−	−	70	−	−
20	33	M	κ	No	↓	+	−	N.A.	−	−
21	70	F	Gλ	No	↓	−	+	N.A.	−	−
22	55	M	λ	Yes	↓	−	+	33	λ	Diffuse
23	62	F	Gκ	No	Normal	−	−	30	−	−
24	55	F	Gκ	No	↓	+	−	55	−	−
25	60	M	Gκ	No	↓	+	−	N.A.	−	−
26	33	M	Gκ	No	↓	−	−	N.A.	−	−
27	35	M	Gλ	Yes	↓	−	+	40	−	−
28	53	M	Gκ	No	↓	−	−	2	−	−
29	60	M	Gκ	No	↓	−	−	30	K	Mild pv.
30	60	M	Aλ	No	Normal	−	−	20	K	−

N.A. – Not available. pv. – perivascular EM – electron microscopic.

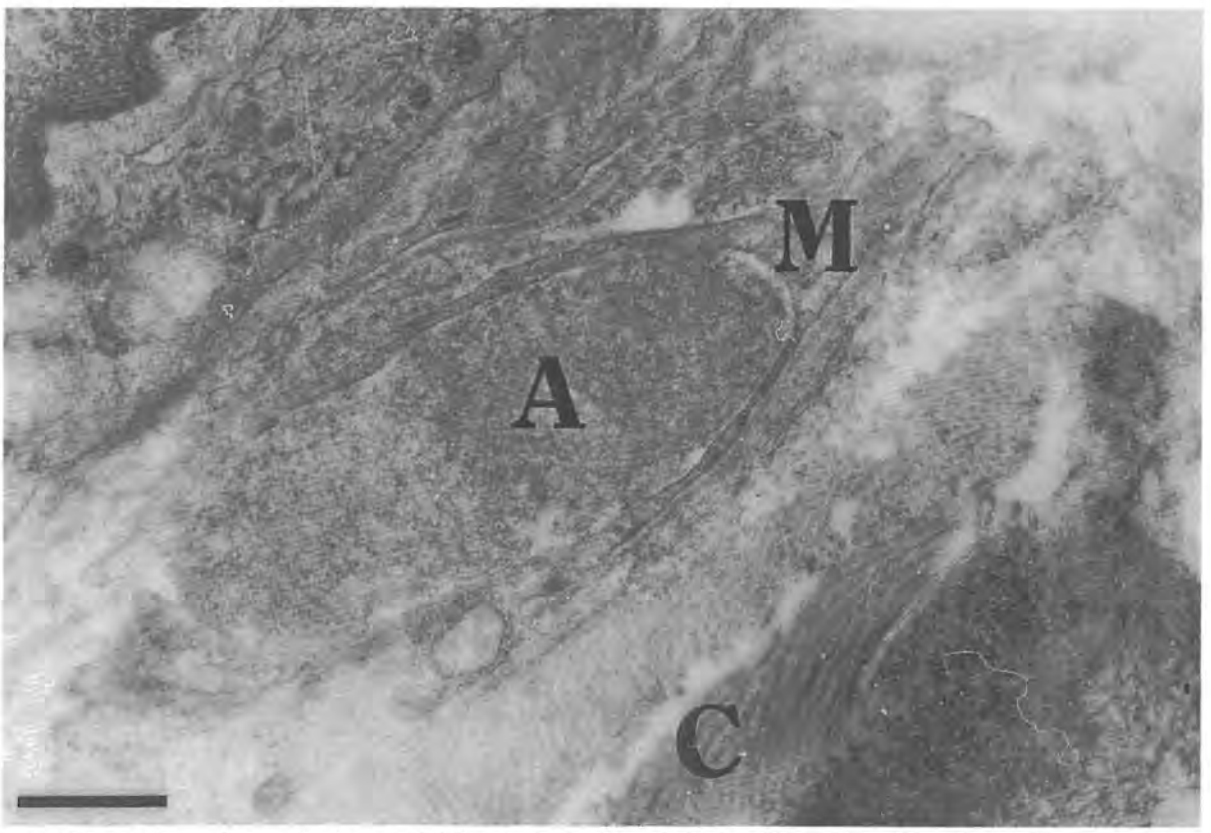

Fig. 1d. Transmission electron micrograph of amyloid (A) deposits in Case 13. Note collagen fibres (C) and cytoplasmic process of macrophage (M). (Bar = 2 μ).

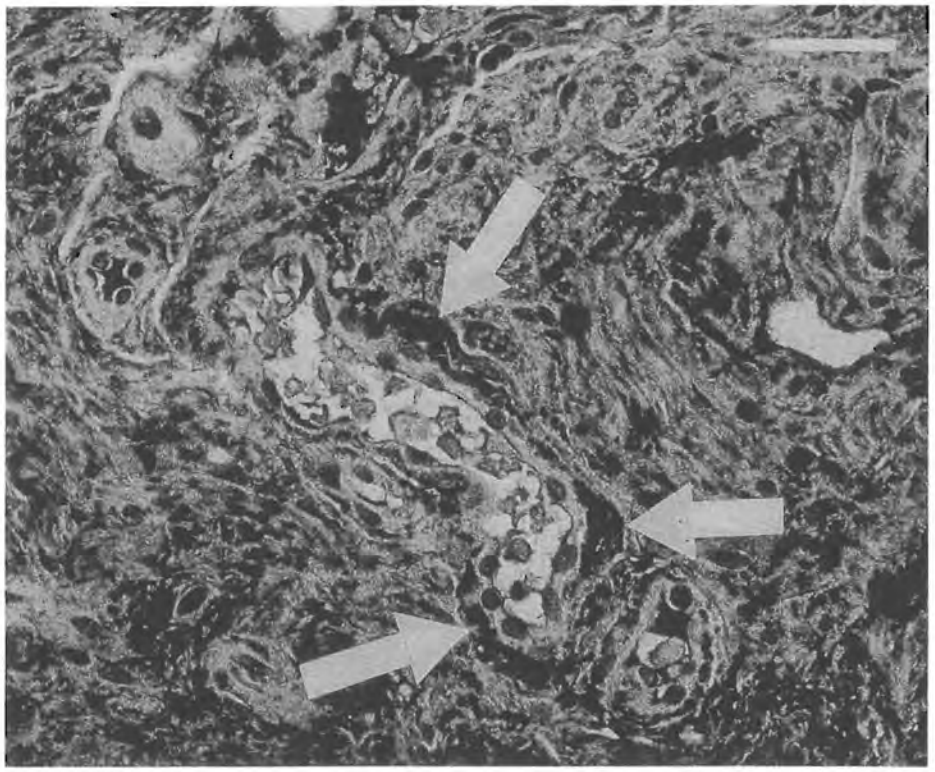

Fig. 2. Immunoperoxidase stain for kappa light chains in Case 29. Note pericapillary amyloid deposits (arrows). (Bar = 40 μ).

successful than biopsies of other areas of the gastrointestinal tract for the identification of amyloid as our incidence of MM-associated amyloidosis of 27% is higher than the 6–15% generally reported in the literature (1, 6, 7). It could be argued that the amyloid deposits in some of our positive cases were unrelated to MM and represented senile amyloidosis, a significant percentage of which is of the AL type (1). This seems unlikely as the AL amyloid

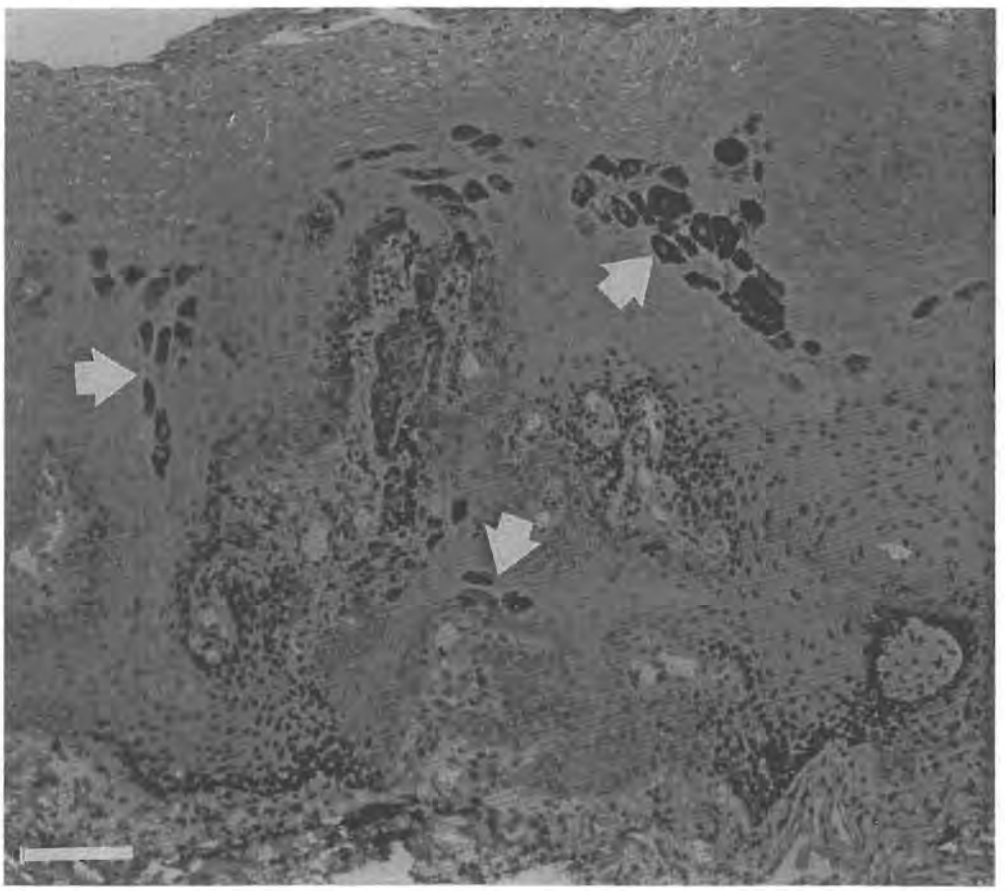

Fig. 3. Immunoperoxidase stain for IgG in Case 6. Note positive staining of focal groups epithelial cells (arrows). (Bar = 100 μ).

subtypes in our study corresponded with the patients' MM secretory type. Furthermore, a recent study (11) failed to identify senile amyloid in tongue biopsies of 94 patients beyond the age of 40 years.

Macroglossia is a feature which has been reported in one fifth of patients with MM-associated amyloidosis (1, 12). Our study indicates that although macroglossia does occur more frequently in MM patients with amyloidosis, tongue enlargement can also be encountered in the absence of amyloid (Table 1). The presence of mucosal nodules covered by an atrophic mucous membrane is probably a more specific clinical sign indicative of amyloidosis of the tongue.

Although EM is the technique of choice for the identification of minute amyloid deposits and intracellular fibrils, LM examination of Congo red stains yields acceptable results. Our study supports the feasibility of kappa and lambda subtyping of AL amyloid with the immunoperoxidase method (13). However, the high concentration of tissue-associated monoclonal immunoglobulin chains or fragments thereof in MM makes identification of amyloid in these sections difficult. The presence of amyloid-associated giant cells which contained light chains, supports the role macrophages play in AL type amyloidogenesis.

The relevant MM secretory type immunoglobulin and light chain in focal groups of epithelial cells in the tongue mucosa is a feature not yet described. Preliminary investigations suggest that spindle-shaped cells in the basal region of the tongue mucosa are involved in the presentation of phagocytosed immunoglobulin chains to the basal epithelial cell layer. Although the significance of this phenomenon is speculative, it may form part of a process of trans-mucosal elimination of excessive proteins and the role of Langerhans cells in this process needs to be investigated.

Only 4 patients in our series had Bence Jones (or light chain secreting) MM and 2 of these exhibited amyloid deposits. It is noteworthy that the amyloid in these 2 cases had a diffuse distribution and contained the most striking macrophage and giant cell reaction.

Our study does not support a higher amyloidogenic potential for lambda light chains, as the majority of deposits were of the kappa type. Furthermore, our youngest patient, Case 17, with a kappa light chain secreting MM presented with the most extensive amyloid deposits of all. Three patients with amyloidosis had no urinary light chains even though extremely sensitive immunochemical techniques were employed for the detection thereof. Urinary light chain excretion is dependent on a variety of factors, of which renal tubular function plays an important role: light chains will be absent from the urine while the ability of the renal tubuli to absorb and catabolize light chains are maintained. We detected light chains in the urine of 11 patients without amyloidosis and, therefore, suggest that the presence of urinary light chains as indicative of co-existing amyloidosis be used with caution.

The association between amyloidosis and a high percentage plasma cells in random bone marrow aspirations or biopsies appears to be inconsistant. Both techniques may fail to identify significant plasma cell levels due to the patchy and often atypical distribution of the tumor mass, as illustrated by our Case 13. The absence of amyloid in patients with 70% or more bone marrow plasma cells in our study further supports our scepticism of this correlation.

Amyloidosis is a recognised and grave complication of MM. As no biochemical or hematological parameter appears to be associated with amyloidosis in MM, we suggest that routine tongue biopsies be performed on patients with MM for the identification and immunochemical subtyping af AL type amyloid.

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Salivary Immunoglobulin Related Proteins in 24 Patients with Multiple Myeloma

Erich Raubenheimer, Willie van Heerden, Joseph Dauth and Tracy van der Walt

Mixed saliva and blood of 24 cases of multiple myeloma (MM) were collected and the immunoglobulin and light chain concentrations compared with that found in the saliva and blood of 16 age matched control patients. The concentrations of salivary IgA, IgG and lambda light chains were significantly increased in IgA-, IgG- and lambda light chain producing MM respectively. Salivary IgA concentration in non-IgA MM and salivary IgG concentration in non-IgG MM were within normal ranges. Despite a significant decrease in circulating normal immunoglobulins, this study fails to support suppression of normal salivary immunoglobulin concentrations in patients suffering MM.
Oral Oncol, Eur J Cancer, Vol. 29B, No. 4, pp. 295-297, 1993.

INTRODUCTION

In the majority of patients with multiple myeloma (MM) serum protein electrophoresis will disclose the presence of a monoclonal paraprotein which may present as an increase in one of the immunoglobulin classes and/or immunoglobulin-related light chains (Bence-Jones proteins). MM are immunochemically typed according to the circulating monoclonal immunoglobulin and/or light chain type produced by the disseminated neoplastic plasma cells. This typing is helpful in predicting complications and prognosis of patients suffering MM [1]. The decrease in the concentrations of circulating normal immunoglobulins predispose to opportunistic infections, a serious and often terminal complication in MM [2].

Reports on the presence of abnormal immunoglobulin-related proteins in secretions of MM patients are infrequent in the literature. Analysis of saliva of 10 patients with MM [3], identified monoclonal IgA in 5 out of 7 patients with IgA MM and monoclonal IgG in both patients with IgG MM. No free light chains were detected in the saliva of the 1 patient with light chain producing MM. An increased concentration of IgG was present in the saliva of 1 case of IgG MM studied by Brandtzaeg [4].

The purpose of this study was to determine the concentrations of immunoglobulins and light chains in saliva and serum of 24 patients with MM and to compare the values obtained with that found in age matched, systemically healthy patients.

PATIENTS AND METHODS

Whole saliva and blood of 24 patients with MM and 16 age matched systemically healthy control patients were collected after a thorough clinical oral examination. The saliva was expressed with the aid of a sterile syringe from a cottonwool swab after it had been chewed for 3 min. Patients with overt signs of gingivitis or periodontitis were excluded from the control group of the study. Quantitation of IgA, IgG and IgM levels in serum were done with rate nephelometry (Auto ICS, Beckman Instruments Inc. Fullerton, U.S.A.). Immunochemical typing of the light chains in serum was carried out with immunofixation electrophoresis (Paragon™ IFE gels, Beckman Instruments Inc.).

Salivary immunoglobulins and light chains were quantitated with low concentration radial immunodiffusion plates (LC-Partigen® and M-Partigen®, Behringwerke AG, Marburg, West Germany). The concentrations were expressed in grams per litre (g/l), compared with the respective circulating concentrations and the findings were subjected to statistical analysis using Student's *t*-test for uncorrelated data.

RESULTS

Clinical examination of the MM patients revealed no signs of oral mucosal infections. 17 patients had IgG MM, 4 IgA MM and 3 light chain producing MM (two kappa- and one lambda MM). The mean concentrations and standard deviations of the major immunoglobulin classes in MM patients and the control group are expressed in Table 1 and the immunoglobulin light chain concentrations in Table 2. The circulating residual immunoglobulin concentrations in MM patients were generally below the normal ranges (Table 3) and that of the control group (Table 1). No significant differences were found between salivary IgA concentrations in non-IgA MM and the control group ($P > 0.05$) and salivary IgG levels in non-IgG MM and the control group ($P > 0.8$). In IgA MM, salivary IgA concentrations were found to be significantly higher than in the control group ($P < 0.01$). A significant increase in salivary IgG in IgG MM ($P < 0.01$ was also present. The concentration of lambda light chains in the saliva of lambda-producing MM was significantly higher than the control group ($P < 0.01$). Although salivary kappa light chain concentrations in kappa-producing MM showed great variations, with single values far above those of control patients, statistical analysis failed to prove a significantly higher concentration of kappa light chains in kappa-producing MM when compared to the control group ($P > 0.05$).

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Table 1. Concentrations of major immunoglobulin types in MM- and control patients

	Saliva g/l		Serum g/l		
	IgG	IgA	IgG	IgA	IgM
IgA MM (2 × IgA κ's 2 × IgA λ's)	0.04 ± 0.03	1.1 ± 0.9	5.85 ± 4.4	41.5 ± 25.3	2.0 ± 3.5
IgG MM (12 × IgG κ, 5 × IgG λ)	0.22 ± 0.16	0.05 ± 0.05	75.9 ± 32.4	0.63 ± 0.6	0.57 ± 0.42
Lambda MM (n = 1)	0	0.14	5.5	0.3	0.2
Kappa MM (n = 2)	0.7 ± 0.01	0.04	13.1 ± 1.5	0.65 ± 0.07	0.25 ± 0.07
Control (n = 16	0.047 ± 0.03	0.081 ± 0.03	20.0 ± 6.6	3.28 ± 1.3	2.16 ± 1.7

Table 2. Light chain concentrations in MM- and control patients

	Saliva g/l		Serum g/l	
	κ	λ	κ	λ
κ-producing MM (n = 16)	0.44 ± 1.0	0.006 ± 0.01	43.5 ± 24.5	2.2 ± 1.8
λ-producing MM (n = 8)	0.03 ± 0.06	0.16 ± 0.12	4.4 ± 2.9	55.1 ± 37.0
Control (n = 16)	0.03 ± 0.03	0.02 ± 0.01	13.4 ± 5.3	7.04 ± 1.5

Table 3. Normal ranges

Serum	
IgG	14.4—22.7 g/l
IgA	1.9—4.7 g/l
IgM	0.7—2.6 g/l
κ	5.66—13.0 g/l
λ	3.04—7.35 g/l
Saliva	
IgA	0.05—0.48 (mean 0.137) g/l*
IgG	0.007—0.037 (mean 0.016) g/l
κ	N/A
λ	N/A

*Grönblad 1981 [5].

DISCUSSION

This study represents the largest series in which the concentrations of immunoglobulin related proteins in saliva of patients with multiple myeloma were determined. Although changes in the circulating immunoglobulin concentrations are well documented [2], little is known of alterations in salivary immunoglobulins and immunoglobulin related proteins in this disease.

A study using immunoelectrophoresis to determine the presence of salivary immunoglobulins in 10 patients suffering MM [3] failed to express the concentrations and the findings can therefore not be compared directly to ours. These authors conclude that although the concentration of monoclonal immunoglobulin is low in saliva, its presence is adequate proof that circulating immunoglobulins can find their way into external secretions. The technique employed in our study is more sensitive and made accurate quantitation of the different immunoglobulin-related proteins possible. All our cases of IgA MM had significantly increased concentrations of IgA in saliva when compared to the salivary IgA concentrations found in the control group. The same applies to salivary IgG in IgG MM and lambda light chain concentrations in the saliva of lambda producing MM. Despite a few kappa producing MM that had high salivary kappa concentrations, statistical analysis failed to support a significant increase in salivary kappa concentrations in kappa producing MM when compared to control values. Although transmission of circulating immunoglobulin related proteins to saliva appears to be enhanced by elevated serum concentrations, no direct correlation could be found between these values.

The occurrence of systemic immune suppression in MM is well documented. This study supports the findings of Coelho *et al.* [3] which failed to identify salivary immunoglobulin impairment in MM. No statistical evidence of a decrease in the concentration of normal salivary IgA in non-IgA MM patients could be found in our study. This was confirmed in that no clinical evidence of an opportunistic infection was seen in the oral cavities of our MM patients. The mechanism by which normal immunoglobulin production is suppressed in MM, is not clearly understood [6]. It has been postulated that neoplastic plasma cells secrete a factor capable of activating suppressor macrophages which in turn inhibit normal B cell function [7]. The observation that salivary gland associated immunoglobulin production is not altered in MM, adds an interesting parameter to the debate on MM-induced immunoparesis.

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