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Primary extramedullary plasmacytoma of the salivary glands

PAUL D. KERR B.Sc., M.D., JOSEPH C. DORT M.D., F.R.C.S. (Winnipeg, Manitoba, Canada)

Abstract
Primary extramedullary plasmacytomas (PEMP) are uncommon plasma cell neoplasms that generally occur in the submucosal tissue of the upper airway. Salivary gland PEMP is an extremely rare condition. This report describes a unique case of PEMP in the parotid gland asociated with pulmonary amyloidosis. A review of all salivary gland PEMP's suggests that they behave similarly to PEMP's in other locations. The treatment of choice for localized disease is radiotherapy which should include regional lymphatics. Local control can be achieved in the majority of cases. The minority of patients develop systemic metastases and die from their disease. Chemotherapy can control disseminated disease and may induce remission.

Introduction

The term extramedullary plasmacytoma (EMP) refers to plasma cell neoplasms which arise outside the bone marrow. These tumours can be primary (PEMP) or secondary depending on whether or not they are associated with multiple myeloma (MM) at the time of presentation. PEMP's are uncommon tumours with a predilection for the head and neck region. The most commonly involved site is the submucosal tissue of the upper airway: particularly the nose, sinuses, and nasopharynx. Very few cases of PEMP involving salivary glands have been reported. In this paper, we present a unique case of salivary gland PEMP associated with pulmonary amyloidosis. A compilation and analysis of all previously reported salivary gland PEMP's follows in an attempt to clarify the aetiology, diagnosis, treatment and prognosis of these tumours.

Case report

A 73-year-old female presented in June 1987, with a one month history of a lump in the left parotid region. The patient first noticed the lump when she experienced left preauricular pain during a meal. Subsequently, she noticed gradual enlargement of the mass. Pain continued to occur whenever she ate acidic foods. The patient reported a similar episode of swelling and pain one year prior to this presentation. The earlier attack had spontaneously resolved within a week.

The past history was significant in that the patient was diagnosed as having pulmonary amyloidosis by open lung biopsy in 1980. The amyloid was of type AL (*i.e.* amyloid due to deposition of immunoglobulin light chain fragments) and stained positively for lambda light chains. A complete work up for multiple myeloma including analysis of serum and urine for abnormal proteins, bone marrow aspiration and biopsy, skeletal survey, and ESR was negative. The patient was treated with colchicine which had to be stopped in 1986 because of the development of hypaesthesiae. Her amyloidosis remained radiologically stable after diagnosis although the patient complained of increasing shortness of breath after discontinuing the colchicine. Her family history was unremarkable.

Physical examination revealed a thin but otherwise healthy looking lady. The left parotid was firm, swollen and slightly tender. Thick, clear fluid could be expressed from Stensen's duct. Facial nerve function was intact. There was no cervical lymphadenopathy. The remaining physical examination was normal. Further investigation included a sialogram which showed a normal duct system displaced by an intraparotid mass, a parotid scan which was unhelpful, and a CT scan revealing a homogeneous tumour mass of the left parotid gland. Fine needle aspiration yielded plasma cells but was considered non diagnostic.

A superficial parotidectomy was carried out and a 4 cm tumour of the lateral lobe removed. The tumour was intimately related to the facial nerve and seemed to go into the deep lobe of the gland. Frozen section at the time of surgery was reported as showing only inflammatory changes. Therefore, the facial nerve was left intact and the deep lobe was not explored. The post-operative course was uncomplicated.

Examination of the permanent sections revealed replacement of the parotid gland by monomorphic sheets of plasma cells and a diagnosis of plasmacytoma was made. No amyloid was found in the specimen. The diagnosis was confirmed with electron microscopy and immunoperoxidase staining which was positive for IgG lambda immunoglobin (Figs. 1–3).

A complete work up for multiple myeloma (as described previously) was again performed and was negative. Thus, the final diagnosis was primary extramedullary plasmacytoma.

The patient subsequently received 5,000 cGy of external beam radiation (Co^{60}) to the left parotid region over five weeks. She has been followed regularly since her treatment and presently (40 month follow-up) remains well without evidence of local or systemic disease. Her serum and urine have remained negative for abnormal proteins. Her amyloidosis has not changed radiologically or symptomatically since the plasmacytoma was removed.

Discussion

A plasma cell neoplasm is a monoclonal proliferation of a B cell that has undergone potentially malignant transformation into a plasmacytoid cell. These neoplasms can manifest themselves as several different clinical entities, all of which are associated with the production of homogeneous immunoglobulin composed of a single class of heavy and light chains or fragments of these components.

Plasma cell malignancies can present in systemic or solitary forms. The vast majority of these neoplasms are cases of

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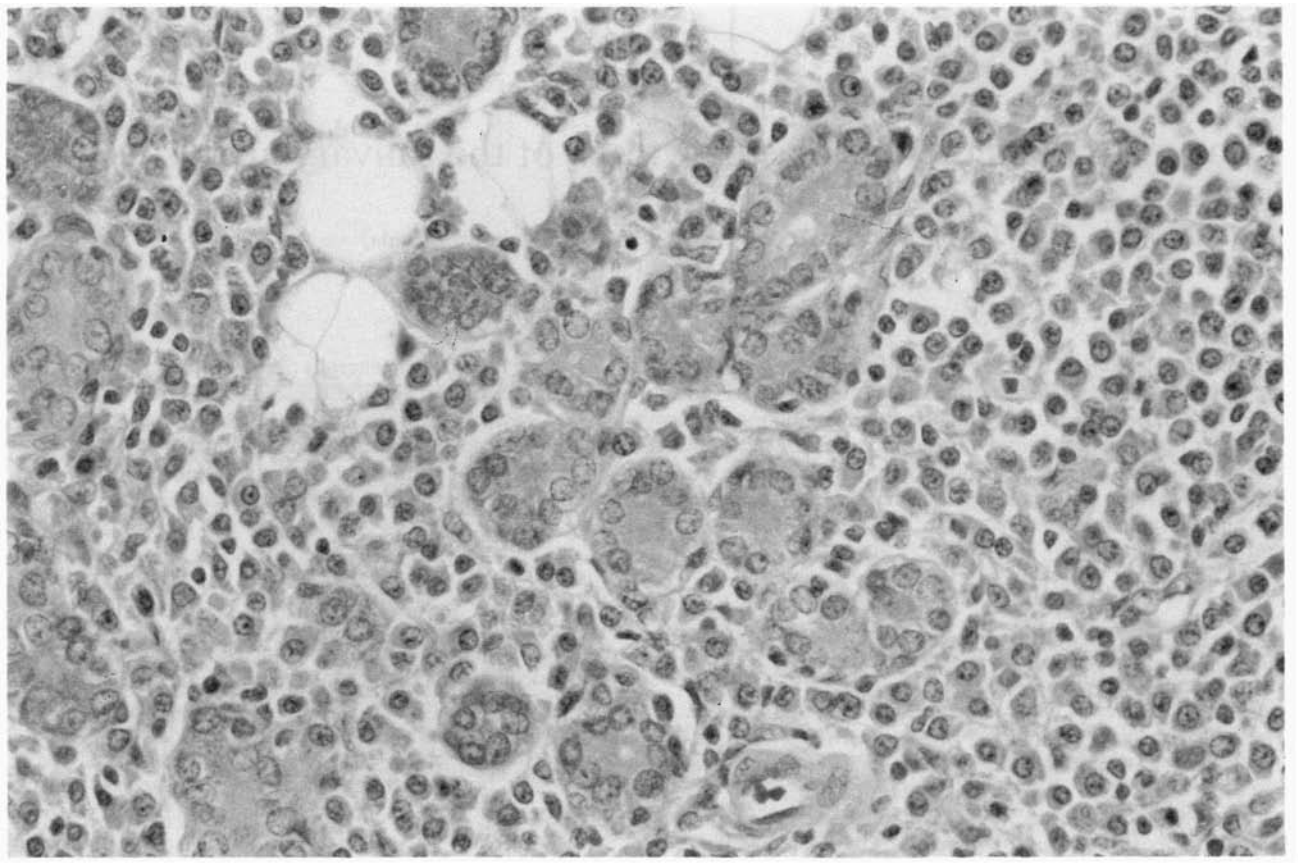

FIG. 1

Medium power view (250×) H&E stained section of tumour showing normal salivary tissue infiltrated by malignant plasma cells.

multiple myeloma (MM). MM is a systemic disease with an incidence of 2.6–3.3 per 100,000 population per year in which malignant plasma cells proliferate throughout the marrow (Bergsagel, 1990). Less than 10 per cent of patients with plasma cell malignancies present with solitary lesions (Salmon and Cassidy, 1989). These solitary tumours can either be in bone (solitary medullary plasmacytoma) or soft tissue (PEMP). Approximately 80 per cent of PEMP's occur in the head and neck region and these cases are generally in the submucosal tissues of the upper respiratory tract (Wiltshaw, 1976). Only 13 cases of salivary gland PEMP have been reported in the literature since the first was described in 1965 by Vainio-Mattila. Our case represents the fourteenth to be reported and is unique because of its association with distant amyloidosis. All 14 cases are described in Table I. Wiltshaw's report (1976) of a salivary gland PEMP lacked sufficient detail to be included in this review.

Classification of Salivary Gland PEMP

The relationship of PEMP's to solitary medullary plasmacytomas and MM remains contentious. Medullary plasmacytomas appear to be an early form of MM and the majority of patients with these tumours will develop and die from systemic disease. PEMP may also represent an early form of MM or it may be a separate disease entity (Wiltshaw, 1976; Woodruff *et al.*, 1979; Corwin and Lindberg, 1979; Kapadia *et al.*, 1982; Batsakis, 1983). Authors who suggest the latter, use several arguments to support their position. PEMP has a much better prognosis than medullary plasmacytoma or MM and the majority of patients (approximately 80 per cent) remain disease-free at periods exceeding 10 years after treatment (Salmon and Cassidy, 1989). Unlike MM, patients with disseminated disease from a PEMP often respond to chemotherapy, occasionally with complete remission (Wiltshaw, 1976). Finally, PEMP's metastasize randomly to soft tissue and bone unlike metastatic medullary plasmacytoma and MM which show a marked preference for the axial skeleton. Evidence supporting each of these points is found in this series of salivary gland tumours. For example, only 3/14 (21 per cent) patients with salivary gland PEMP developed widespread metastases and two died of their disease. Case 4 represents a patient who had a remission of metastatic disease induced by chemotherapy and subsequently lived eight years. Finally, the pattern of metastases in case 4 was predominantly that of soft tissue involvement.

Aetiology and Pathogenesis of Salivary Gland PEMP

The aetiology of PEMP is unknown. Although genetic factors, radiation, various occupational exposures and chronic antigenic stimulation are all proposed risk factors for the development of plasma cell neoplasms, it is difficult to prove these associations (Bergsagel, 1979). Little information exists on risk factors specific to solitary placmacytomas. Villanueva *et al.* (1990) reported the development of a PEMP in the left submandibular gland of a patient with Sjögren's syndrome (Case 12). The evolution of lymphoma and other malignancies in patients with Sjögren's syndrome is well known, but the pathogenic mechanisms remain unclear.

Approximately 10–20 per cent of PEMP's present with multiple local tumours. Similarly, 14 per cent (2/14) of salivary gland PEMP's had multiple gland involvement. Whether multicentric cases represent metastases or multiple primaries is unknown. Only detailed serum and tumour protein studies will answer this question. Confirmation of multiple primaries would indicate the existence of an aetiological factor capable of causing a diffuse field change.

Epidemiology

PEMP's in general occur three to four times more frequently

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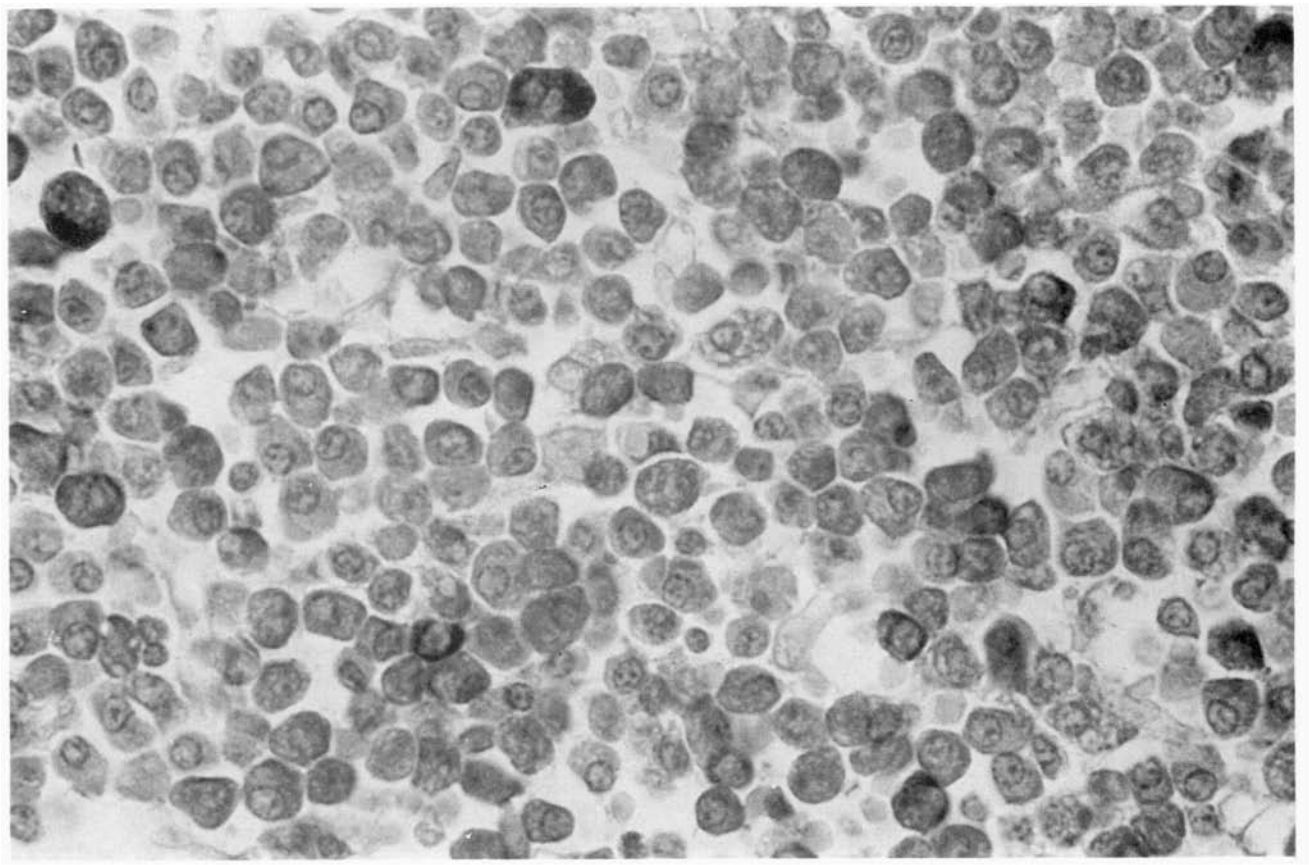

FIG. 2

High power view (400×) immunoperoxidase stain of tumour showing positive staining for IgG lambda.

in males (Wiltshaw, 1976; Kapadia *et al.*, 1982). The sex distribution of salivary gland PEMP's is roughly equal (8 males, 6 females). The age distribution at diagnosis of patients with salivary gland PEMP is similar to that of patients with PEMP in other sites. The majority of patients are diagnosed between the ages of 50 and 70 years and the median age at diagnosis is approximately 65 years (Wiltshaw, 1976; Bergsagel, 1990).

Clinical Presentation

In general, patients with salivary gland PEMP's present with a firm, non-tender, enlarging mass in the involved gland. Two patients complained of associated pain. In our patient this appeared to be due to partial intrinsic duct obstruction. One patient presented with bloody otorrhoea and hearing loss secondary to an extensive parotid tumour. The function of the facial nerve was not affected in any case. The duration of the lesion at presentation was generally a few months but ranged from weeks to five years.

Of the 14 salivary gland tumours reported, 71 per cent (10/14) were located in the parotid gland, 14 per cent (2/14) were in the submandibular land and 14% (2/14) were in multiple glands.

Diagnosis

Diagnosis of salivary gland PEMP's is difficult and many of the initial diagnoses are incorrect. Difficulties arise because these tumours are rare, often lack characteristic clinical features and are a challenge to the pathologist. Only two patients had clinical features that should have raised suspicion for a tumour of immunocyte origin: Case 12 with Sjögren's syndrome (Villanueva *et al.*, 1990) and the subject in our case report with associated pulmonary AL amyloidosis. AL amyloidosis represents an accumulation of immunoglobulin light chain fragments in various organs. Its development indicates the presence of a clone of cells producing amyloidogenic light chains and is a cue to initiate a work up ruling out the presence of a lymphocyte or plasma cell malignancy. Although local amyloid deposition occurs in approximately 15 per cent of cases of PEMP, remote amyloid deposition is very rare and has never before been reported with a salivary gland PEMP (Zaslow and Staub, 1969; Batsakis, 1983). In our patient, initial investigations failed to detect an underlying immunocytic neoplasm and she finally presented seven years later with a PEMP. Screening of serum and urine in patients with PEMP is often negative because the tumours are not large enough to produce detectable levels of paraprotein.

Salivary gland PEMP's are challenging to the pathologist because they have variable histological features, can be poorly differentiated, and can have clinical and histological features similar to other lesions. Frozen and permanent sections of these tumours have been mistaken for sarcoid (Pahor, 1977), undifferentiated carcinoma (Pascoe and Dorfman, 1969) and inflammatory lesions (Koop and Carley, 1976; Palestro *et al.*, 1983) resulting in incorrect initial histological diagnoses in 36 per cent (5/14) of cases.

Histological differential diagnosis of these lesions would include other malignant processes such as lymphoma, undifferentiated carcinoma, and melanoma (Kapadia *et al.*, 1982; Palestro *et al.*, 1983); and benign processes such as plasma cell granuloma and pseudolymphoma. Electron microscopy and immunohistochemical stains that detect the monoclonal antibodies produced by these tumours are invaluable for differentiating plasmacytomas from these other conditions (Kapadia *et al.*, 1982).

There is little information available on the accuracy of cytology in the diagnosis of PEMP. Although a fine needle aspiration biopsy (FNA) was thought to be non-diagnostic in our patient, a recent report by Das *et al.* (1986) indicates the potential usefulness of FNA in cases of plasma cell tumours.

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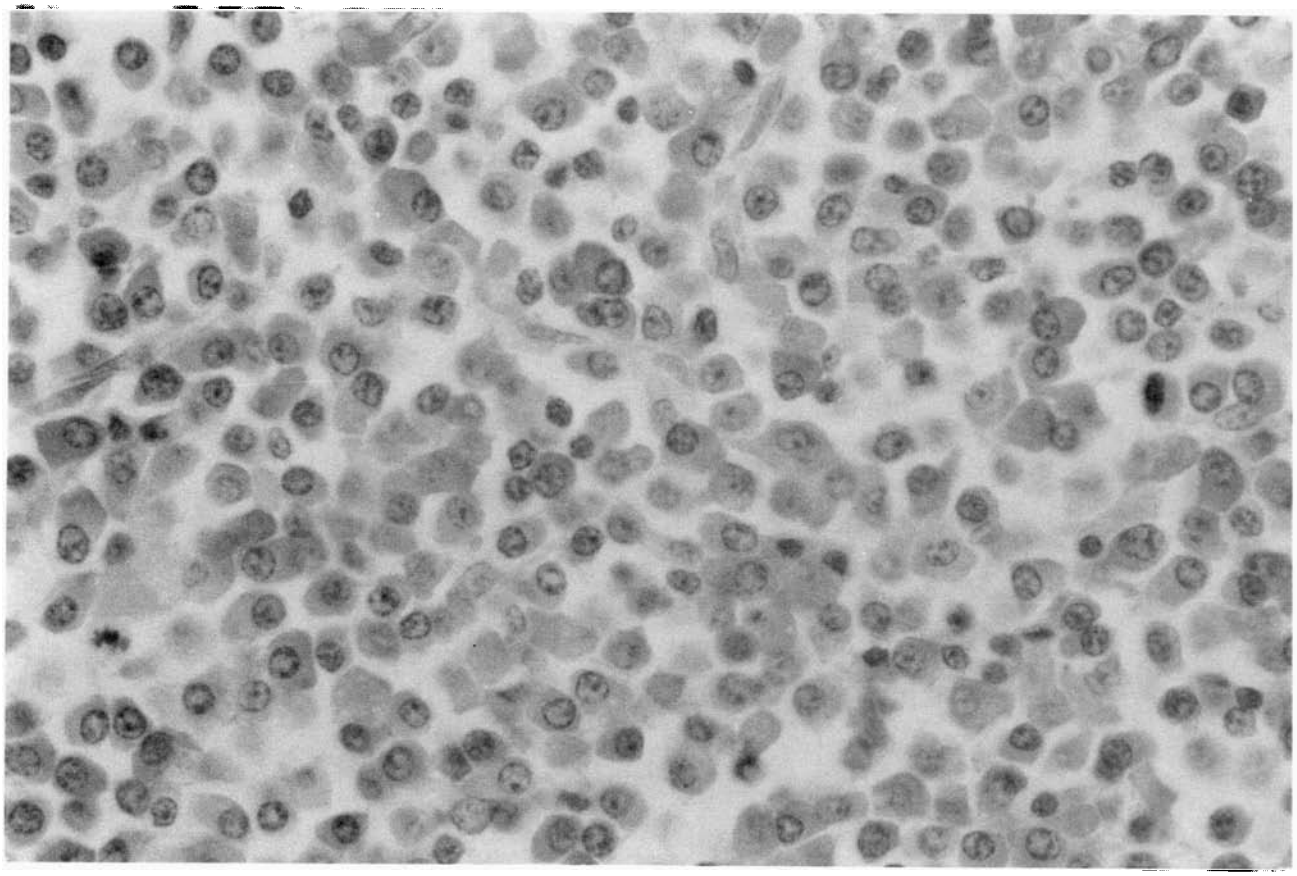

FIG. 3

High power view (400×) immunoperoxidase stain of tumour showing negative staining for IgG kappa.

Treatment and Prognosis

Radiotherapy is the treatment of choice for PEMP's (Abemayor *et al.*, 1988). Several studies indicate that local control rates of >80 per cent are obtained with radiotherapy (Corwin and Lindberg, 1979; Wodruff *et al.*, 1979; Harwood *et al.*, 1981; Mayr *et al.*, 1990). The median survival is >5 years and approximately 16 per cent of patients go on to develop systemic disease (Mayr *et al.*, 1990). Death from PEMP is generally due to systemic metastases. Complication rates from radiotherapy are low. Although some centres suggest that doses as low as 3,500 cGy are effective (Knowling *et al.*, 1983), most would recommend 4,000–5,000 cGy over 4–5 weeks. Approximately a quarter of patients with PEMP of the head and neck will develop regional lymph node metastases. Therefore, recent studies have recommended the addition of elective regional lymphatic irradiation (Harwood *et al.*, 1981; Mayr *et al.*, 1990).

Salivary gland PEMP's present an interesting problem because the tumours are often totally removed as excisional biopsies (*i.e.* superficial parotidectomy or submandibular gland excision). This raises the question of whether any further treatment is needed in the form of radiotherapy. We believe post-operative radiotherapy is warranted in these patients for the following reasons. The overall local recurrence rate of salivary gland tumours was 14 per cent (2/14). Both of these patients had been treated with surgery alone. The proportion of patients with salivary gland PEMP's that develop either local lymph node metastases (29 per cent) or systemic disease (21 per cent) is similar to that quoted for PEMP's in other sites (Knowling *et al.*, 1983; Mayr et al., 1990). The propensity of salivary gland PEMP's to spread to local lymph nodes supports the recent recommendation for elective regional lymphatic irradiation. Finally, this disease has a potentially good prognosis, therefore, initial treatment should be aggressive.

Treatment of systemic metastases from PEMP is worthwhile. Chemotherapy can result in long-term control and even remission of disseminated disease (Wiltshaw, 1976). Case 4 represents an example of this phenomenon. Alkylating agents are the mainstay of therapy.

Attempts have been made to correlate various histological and clinical features of PEMP's such as cellular differentiation, bone invasion, nodal metastases, and immunoglobulin production with prognosis (Corwin and Lindberg, 1979; Harwood *et al.*, 1981; Kapadia *et al.*, 1982; Batsakis, 1983; Mock *et al.*, 1987). These results are controversial. In the group of salivary gland tumours, patients who presented with more extensive disease fare poorly. The three patients who developed systemic disease had either metastatic or extensive local disease at the time of diagnosis. All patients who went on to develop systemic or recurrent disease did so within 13 months. This is consistent with other series indicating that almost all patients with PEMP that go on to develop systemic disease do so within two years of diagnosis (Kapadia *et al.*, 1982; Mayr *et al.*, 1990). These facts lend some degree of predictability to the course of individual patients.

After their initial treatment, patients with salivary gland PEMP's must undergo regular lifelong follow-up to watch for local recurrence, metastases, and associated complications such as amyloidosis. In patients who develop systemic metastases, the tumour load is generally large enough to produce detectable levels of paraprotein in the serum and urine. Therefore, screening tests for abnormal proteins are useful for early recognition of systemic disease. The risk of developing amyloidosis increases as tumour load increases. However, cases such as ours demonstrate that even small, solitary plasmacytomas can cause systemic amyloid deposition.

Conclusion

PEMP's are rare plasma cell neoplasms that usually present in the submucosal tissue of the upper airway. These tumours

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TABLE I

Case	References	Sex/age	Site(s) at diagnosis	Amyloid	Treatment	Course
1.	Vainio-Mattila (1965)	F/74	Left parotid gland with parapharyngeal extension	—	Surgery Radiotherapy	A&W 11 mon
2.	Koop and Carley (1966)	M/73	Left submandibular gland	—	Surgery	Recurrence in left parotid and regional node treated with surgery. ID 36 mon
3.	Pascoe and Dorfman (1969)	M/50	Right submandibular gland Regional nodes	—	Surgery	AWD 8 months
4.	Pahor *et al.* (1977)	F/61	Right parotid gland Both submandibular glands Regional nodes and mediastinum	—	Surgery Chemotherapy	DDD 110 months
5.	Pahor (1977)	M/89	Left parotid gland	—	Radiotherapy	ID 34 mon without recurrence
6.	Ferlito *et al.* (1980)	M/47	Left parotid gland	Local	Surgery Radiotherapy Chemotherapy	A&W 6 months
7.	Kanoh *et al.* (1985)	F/78	Left parotid gland with parapharyngeal extension	Local	Surgery	Recurrence locally and in regional nodes treated with radiotherapy. A&W 7 mon
8.	Edney *et al.* (1985)	M/38	Right parotid gland	—	Surgery	A&W 2 months
9.	Scholl and Jafek (1986)	F/60	Left parotid gland	—	Surgery Radiotherapy	A&W 12 months
10.	Ebbers (1986)	M/68	Left parotid gland with parapharyngeal extension	—	Radiotherapy	DDD 12 months
11.	Simi *et al.* (1988)	M/58	Right parotid gland	—	Surgery	A&W 72 months
12.	Villanueva *et al.* (1990)	F/64	Left submandibular gland		Radiotherapy	No follow-up available. Known Sjogren's syndrome
13.	Rothfield *et al.* (1990)	M/53	Left parotid gland	—	Surgery	A&W 26 months
14.	Present report	F/73	Left parotid gland	Pulmonary	Surgery Radiotherapy	A&W 40 months

A&W—alive and well.
AWD—alive with systemic disease.
DDD—dead from systemic disease.
ID—dead from intercurrent disease.

can originate in the major salivary glands and, when they do, seem to behave similarly to other head and neck PEMP's. The aetiology and pathogenesis of salivary gland PEMP's is unclear but their association with conditions such as Sjögren's syndrome may provide some clues in the future. Evidence in this series of salivary gland tumours supports the theory that PEMP is a separate disease entity, not part of the multiple myeloma disease spectrum. The treatment of choice for salivary gland PEMP is radiotherapy. Local control is achieved in >75 per cent of patients. These tumours often metastasize to local lymph nodes thus regional lymphatics should be electively irradiated. Death from this disease is due to systemic metastases which occur in 1/4 of the patients. Chemotherapy can control disseminated disease and may induce remission.

Once PEMP of the salivary glands is diagnosed, efforts must be made to rule out systemic complications. Regular follow-up should be continued indefinitely to watch for the development of metastatic disease. AL amyloidosis may be a rare systemic complication of PEMP.

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Address for correspondence:
Dr. P. Kerr,
61 Emily Street,
Winnipeg,
Manitoba R3E 1Y9,
Canada.

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