Simultaneous bilateral pleomorphic adenomas of the parotid glands with unilateral tyrosine rich crystalloids

A T Warfield, L A Smallman

Abstract

A case of simultaneous, bilateral pleomorphic adenoma of the parotid glands following irradiation to the head and neck for childhood Hodgkin's disease is presented. The tumour on the side given the highest radiation exposure contained so-called tyrosine rich crystalloids (TRCs). Simultaneous salivary gland neoplasms are rare; TRCs are also an unusual finding. Simultaneous pleomorphic adenomas with TRCs confined to one tumour have never been described, and any association between TRCs and irradiation has never been commented on.

The precise nature of the TRCs remains obscure. Their unilateral distribution in this case supports the hypothesis that local factors are more important in their formation than systemic factors. In conjunction with other published work, this provides circumstantial evidence that irradiation may predispose to TRC deposition.

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Tyrosine rich crystalloids (TRCs) have been described in various neoplasms of the major and minor salivary glands, with isolated examples in ceruminous and lacrimal gland tumours and in fibrous tissue in laryngectomy specimens. They may be seen in both histological sections and in cytological preparations but are not apparent macroscopically. They most commonly occur in pleomorphic adenomas, usually of the parotid gland. Personal experience and most studies suggest that TRCs may be demonstrated in approximately 1.5-5% of pleomorphic adenomas, although an incidence of 21% in tumours from African patients is reported in one study.¹

Multiple, separate neoplasms of the salivary glands are unusual. Simultaneous neoplasms of two or more major salivary glands are more common than multiple, unilateral cases, with an incidence of around 0.4% for all tumour types. Of these, Warthin's tumour is the most common with over 100 reported cases, followed by pleomorphic adenoma with around 34 cases.² Irradiation of the head and neck increases the risk of developing subsequent salivary neoplasms, and patients with radiation related salivary gland tumours experience a high rate of second

tumours of salivary, thyroid, and parathyroid glands.³

To these authors' knowledge, simultaneous pleomorphic adenomas with TRCs confined to one neoplasm have never been described. Furthermore, any association between TRCs and irradiation of the head and neck has not previously been commented on.

Case report

A 41-year-old white man was referred for further investigation of painless, bilateral facial swelling. He was otherwise in good health but had a history of Hodgkin's lymphoma, which was diagnosed at the age of 12 years and had been treated with radiotherapy to cervicofacial fields. Over the following nine years relapse confirmed by biopsy occurred, followed by further radiation to the mediastinum and abdomen. Since that time he had been in clinical remission.

The right facial lump was in the region of the tail of the parotid gland and was first noticed three years previously. Initially, this was thought to represent another relapse of the Hodgkin's disease and radiotherapy was given empirically to the right side of the face after one year. Despite this, the lump continued to enlarge slowly over the next two years and, in addition, a similar left preauricular swelling became apparent. There was no other evidence to suggest relapse of Hodgkin's disease and therefore excision biopsy of both lesions was performed. The patient made an uneventful recovery.

Pathological findings

The right superficial parotidectomy specimen consisted of normal looking salivary gland with a 2.5 cm diameter, well circumscribed lesion towards one edge. This showed a solid, cream cut surface. The left lumpectomy specimen consisted of multiple cream tissue fragments, together measuring 1 cm in maximum dimension. All of the tissue was submitted for histological examination and multiple levels were cut through each block.

Microscopically, both specimens showed the typical heterogeneous appearances of pleomorphic adenomas. Myxoid stroma of low cellularity and more densely cellular areas were admixed in roughly equal proportions. The cellular areas showed a diverse pattern with solid sheets and anastomosing cords of epithelial cells, occasional clear cells, scattered groups of cells with a "plasmacytoid"

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appearance, and frequent duct like structures of varying size. The myxoid areas contained individual stellate and fusiform cells in a loose connective tissue background showing focal chondroid differentiation and patchy dystrophic calcification.

In addition, in the right side tumour there were localised collections of weakly refractile, non-birefringent crystal like structures (fig 1). These were present focally within the myxoid stroma in one of the four blocks. They were arranged either singly or in small aggregates and some appeared to have been fractured during tissue sectioning. Individual crystalloids were ovoid or round in outline and averaged approximately 30–45 μm in diameter. They contained a sometimes indistinct, rounded core from which radiated multiple “floret like” or “rosette like” projections, giving a roughly symmetrical, lobulated contour. These structures were lightly eosinophilic, stained bright yellow-orange with Masson trichrome and Van Gieson preparations, and gave a deep purplish-red colour with the diazotisation coupling

method for tyrosine (fig 2), consistent with TRCs. The surrounding salivary tissue showed mild fatty replacement but no other abnormality. The left side tumour showed similar histological features but without crystalloids. There was no evidence of Hodgkin's lymphoma.

Discussion

The pathogenesis and full importance of TRCs are largely unknown. They classically show positive results with the Millon reaction or diazotisation coupling method, indicating that tyrosine is present. Although originally thought to represent pure tyrosine crystals, a variety of techniques have subsequently demonstrated an amorphous polypeptide structure with a relative molecular weight in the region of 17 000.⁴ This has a complex amino acid composition which, in addition to tyrosine, is also rich in arginine, tryptophan, and sulphhydryl groups, and contains trace amounts of calcium, magnesium, and phosphorus.⁵ They show negative staining for collagen, although reticulin is present centrally and between individual “petals”, and are refractile but not birefringent.⁶

TRCs should not be confused with morphologically similar collagenous crystalloids (stellate fibrillar formations), calcium oxalate crystals, or other poorly characterised intraductal crystalloids. Collagenous crystalloids are Millon/diazotisation negative, collagen positive, and weakly birefringent. Calcium oxalate crystals are Millon/diazotisation negative and collagen negative, but strongly birefringent. The diazotisation coupling method obviates the handling and disposal of toxic mercuric reagents used in the Millon reaction⁷ and is therefore preferred in the authors' laboratory.

The previous therapeutic irradiation to the head and neck in this patient is a known risk factor for salivary gland neoplasia. It has been suggested that lower doses of radiation such as those used in certain diagnostic imaging techniques may also be tumourogenic to salivary tissues.⁸ The exposure effects are cumulative and the risk increases with dose. That the TRCs in this case were found only in the neoplasm given the highest radiation exposure may not be entirely coincidental. Several authors do mention previous radiotherapy⁹ or imaging procedures, such as full mouth dental radiography,¹⁰ in their TRC case reports, but make no comment as to any pathogenetic link. Although many of the patients described in the larger series would be expected to have had therapeutic or diagnostic irradiation, the cases are documented in insufficient detail to confirm any association.

Several tentative hypotheses to explain TRC formation have been proposed in the past. These include a defect of pigment metabolism, particularly as TRCs seem to be more common in pigmented races and salivary tyrosine secretion in albino people is reduced. Disordered protein synthesis

Figure 1 Individual, slightly refractile tyrosine rich crystalloid showing a typical “floret like” appearance (haematoxylin–Van Gieson).

Figure 2 Individual tyrosine rich crystalloids showing a positive diazotisation coupling reaction.

by tumour cells or local changes in the concentration of mucopolysaccharides and inorganic ions in the matrix have also been suggested. Histological changes are usually not seen in salivary tissue following low dose radiation exposure. However, TRC deposition may be a more subtle indication of damage following higher doses of irradiation. Other local and possibly systemic factors might also be expected to contribute. The focal distribution of crystalloids in this case might suggest that local variables within an individual tumour may be important, in addition to differences between left and right sides. The precise details of any mechanism, however, remain obscure and purely speculative.

In conclusion, these findings provide circumstantial evidence to support the hypothesis that deposition of TRCs in salivary neoplasms is influenced more by local than by systemic factors. Furthermore, it is proposed that irradiation of the head and neck may be one predisposing factor in TRC formation, an observation that has not previously been made, and that crystalloid deposition may be a subtle reflection of radiation induced damage in some cases.

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CD4+ lymphocytopenia due to common variable immunodeficiency mimicking AIDS

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Abstract

There are an increasing number of published reports of patients with acquired immunodeficiency without evidence of HIV infection, who have been labelled as having "idiopathic CD4+ lymphocytopenia". The case is reported here of a young man who presented with *Pneumocystis carinii* pneumonia (PCP), CD4+ lymphopenia, and hypogammaglobulinaemia attributable to common variable immunodeficiency (CVID). The presentation of this condition, with many of the clinical and laboratory features of AIDS, highlights CVID as a diagnosis to be considered in the differential diagnosis of CD4+ lymphocytopenia.

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Recent reports have described cases of acquired immunodeficiency without evidence of infection by HIV. However, other diag-

noses can mimic the clinical characteristics of AIDS and must not be overlooked. A case of *Pneumocystis carinii* pneumonia (PCP) is reported here in a young, single man who presented with weight loss, generalised lymphadenopathy, and lymphopenia, and who was persistently HIV negative.

Case report

A previously fit 37 year old man presented in October 1989 with a two month history of pruritis, night sweats, and cough. He was unmarried, heterosexual, and denied any homosexual contact, drug abuse, or travel overseas. On examination he had bilateral axillary and supraclavicular lymphadenopathy and hepatosplenomegaly. He declined further investigation. Six months later he returned with symptoms of anorexia, 20 kg weight loss, productive cough, and breathlessness. He was cachectic, febrile (38°C), tachypnoeic, and had bilateral inguinal lymphadenopathy. Chest examination showed bilateral crackles

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