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Case Report

Inflammatory Myofibroblastic Tumour of the Submandibular Gland

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ABSTRACT

A 77-year-old man presented with a two-month history of a left sided, firm, and non-tender submandibular mass. The patient was systemically well with no history of weight loss or night sweats. On examination, there were no oropharyngeal abnormalities and flexible nasendoscopy was normal. An ultrasound scan and magnetic resonance imaging (MRI) confirmed a 2.8 x 2.4 x 4.3cm irregular mass in level I of the neck with a chain of small lymph nodes. Following inconclusive fine needle aspirations (FNA) and a core biopsy, an excision of the submandibular gland was performed. The pathology revealed an inflammatory myofibroblastic tumour (IMT) of the submandibular gland. To complete treatment a selective neck dissection and post-operative radiotherapy was performed. IMTs are rare, poorly understood tumours that can occur anywhere in the body. The incidence in the head and neck regions accounts for a small number of all cases. We present a rare case of IMT in the submandibular gland.

Inflammatory myofibroblastic tumour (imt)

IMTs are rare, benign tumours of unknown cause which have previously fallen under various terms, namely inflammatory pseudotumours, fibrous xanthoma, plasma cell granuloma, pseudosarcoma, myxoid hamartoma, and most recently, inflammatory myofibroblastic tumour (IMT). Although they occur primarily in the lung and orbits, they have been reported to occur in various tissues and organs throughout the body [1]. IMTs provide a diagnostic challenge as biopsies tend to be inconclusive and a diagnostic tissue specimen is required for histological confirmation [2]. Almost any area can be affected by IMTs, but they are most commonly found in the lung and orbits, with head and neck IMTs only representing approximately 14-18% of all cases. Most patients with IMT have a good prognosis and are cured by resection. However, in some cases, IMTs can be locally aggressive, recur and a few cases can undergo malignant transformation [1]. IMTs most commonly affect children and teenagers but have been reported in elderly patients when salivary glands have been affected [3].

IMTs consist of spindle-shaped myofibroblasts infiltrated by inflammatory cells [4]. A storiform or fascicular arrangement of the spindle-shaped cells is seen in a myxoid to hyaline stroma. This arrangement usually contains a variable degree and arrangement of lymphocytes, plasma cells, histiocytes and eosinophils [5]. The spindle cells of IMTs are strongly immunoreactive for vimentin whereas the immunoreactivity for smooth muscle actin and desmin is variable [6]. The management of IMTs varies widely due to the rarity of the tumour and the lack of evidence and treatment protocols. Currently, the literature supports surgical excision as the mainstay of treatment with adjuvant radiotherapy for more aggressive IMTs [6]. Local recurrence is well known, but the risk of distant metastasis is small [3].

Case presentation

A 77-year-old male was referred to his local ENT department with a firm, non-tender left submandibular mass. The patient felt well in himself and described normal taste, appetite and swallow, with no history of night sweats and stable weight. The swelling was firm on palpation, the overlying skin was normal, and the lump was non-tender in nature. Although, the patient did report to having longstanding left sided intermittent otalgia for many years. The rest of the history was unremarkable. On examination, a 2 x 3cm hard non-tender left submandibular mass was palpated in the neck with no other palpable neck lymphadenopathy. The facial nerve was intact and there were

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normal tongue movements. There were no other lesions on oral examination and Wharton's duct appeared patent. Flexible nasendoscopy of the nasopharynx, base of tongue, hypopharynx and larynx were normal.

Investigations

Two ultra-sound guided FNA biopsies of the left submandibular gland were performed but were non-diagnostic. MRI of the neck confirmed a 2.8 x 2.4 x 4.3cm irregular mass in level I of the neck with further subcentimeter lymph nodes in level II, III and IV of the neck. A further ultrasound-guided core biopsy of the submandibular gland and an FNA of a left level II lymph node were performed. The core biopsy was inadequate, but cytology from the level II lymph node suggested the possibility of a low-grade lymphoid neoplasm. To gain a definitive diagnosis, excision of the left submandibular gland was performed under general anaesthesia. Subsequent microscopic appearance of the gland revealed a mass consisting of lobulated, asymmetrical, non-encapsulated, proliferative spindle cells in fascicular arrangements. This tissue contained chronic inflammatory cells and atrophic salivary parenchyma with prominent newly formed lymphoid follicles with germinal centres (B-cells) with invasion into adjacent fat around the submandibular salivary gland.

Immunohistochemically, the proliferative spindled cells were anaplastic lymphoma kinase-1 (ALK-1) positive, smooth muscle actin (SMA) positive, desmin negative and CD68 positive. Adjacent submandibular gland tissue showed established chronic obstructive adenitis with prominent newly formed B-cells. The lymph nodes excised showed non-specific reactive changes. In conclusion, the macroscopic, histological and immunohistochemical features observed in the specimens supported a diagnosis of inflammatory myofibroblastic tumour involving the submandibular gland. The patient was presented in the local Head & Neck Oncology Multi-Disciplinary Team (MDT) meeting as well as the sarcoma MDT. The MDT meetings concluded that the final diagnosis was a T2b N1 M0 inflammatory myofibroblastic tumour.

Differential diagnoses of submandibular gland swellings

The differential diagnoses of submandibular masses are extensive. Benign conditions include infective causes (sialadenitis) which can be secondary to sialolithiasis or systemic inflammatory conditions. The majority (80%) of salivary gland tumours arise in the parotids and 80% of these tumours are benign [7]. Tumours in the submandibular gland (SMG) are rare and 50% of tumours in the SMG and minor salivary glands are malignant [7].

Table1: Common Submandibular Tumours (13).

Histology	**Incidence**
Pleomorphic adenoma	36%
Adenoid cystic carcinoma	25%
Mucoepidermoid carcinoma	12%
Carcinoma ex-pleomorphic adenoma	10%
Adenocarcinoma	7%
Squamous cell carcinoma	7%
Acinic cell carcinoma	1%

Further treatment

The MDT decision recommended a selective neck dissection (levels I-IV) with further discussion. A selective neck dissection was performed but did not reveal any residual malignancy. Several of the dissected nodes showed capsular thickening and minor peripheral replacement of the lymphoid parenchyma. Both the thickening and parenchymal replacement outlined had been affected via fibrosis with a lymphoplasmacytic inflammatory cell infiltrate but lacked expansive qualities. On these grounds, although their presence is somewhat unusual, it is unlikely that the changes reflected expansive metastases of an inflammatory myofibroblastic tumour. These pathology results were discussed in a subsequent MDT meeting and post-operative adjuvant radiotherapy was recommended. A 6-week radiotherapy course of 60 Gy in 30 fractions was completed. Follow-up was planned for 5 years.

Following the radiotherapy treatment, the patient developed a right submandibular and left parotid gland swelling. Core biopsies revealed cores of salivary tissue with atrophic lobules and a diffuse infiltrate of lymphocytes and plasma cells with scattered myofibroblasts with plump nuclei and prominent nucleoli. Immunocytochemistry showed scattered IgG4 positive plasma cells. An autoimmune screen was positive for Anti-Ro, Anti-La, Anti Jo-1 and ANA positive. IgG4 level was 0.8, ACE levels 68, C-ANCA negative. The patient was seen by the rheumatology specialists and was initiated on a course of steroids. The symptoms responded well to steroids however arthralgia and soft-tissue hand swelling subsequently developed. The diagnosis of IgG4 disease was established after multiple biopsies and the patient remains under the care of rheumatologists. The patient has been continuing with long term steroid therapy, with the possibility of commencing Azathioprine or Cyclosporine if the disease remains stable.

Discussion

IMTs in the head and neck region are rare with the specific incidence of submandibular gland IMTs not being clear. Lymphocytes, plasma cells, histiocytes, fibroblasts and myofibroblasts are the basic components of IMT, present in variable proportions [8]. The aetiology and pathogenesis of IMTs remains unclear. The discovery of a genetic link with ALK gene rearrangements located on chromosome 2p23 have been found in 50% of IMT cases. Other hypothesis is that IMTs arise as an immunologic host reaction to stimuli such as microorganisms, tissue damage, foreign bodies or neoplastic tissue [1]. Literature states that the main treatment of IMTs in the head and neck region is surgical excision with negative margins. Post-operative radiotherapy has been used to treat high-risk or aggressive IMTs [1]. Corticosteroids have also been used in addition to excision or when excision has been unsuccessful or not possible [4].

Clinically, IMT is a painless, indurated mass or swelling of short duration. In the head and neck case reports in the parapharyngeal spaces, maxillary sinuses, epiglottis and oral cavity are well documented [4]. Radiologically, IMTs of the head and neck tend to be non-specific, only showing lesion size or infiltrative or aggressive behaviour [8]. Histologically, IMTs are characterised by a variable cellular spindle proliferation in myxoid to collagenous stroma intermixed with acute and chronic inflammatory cells [5]. Coffin et al. described three basic histological patterns

1. myxoid/vascular pattern;
2. compact spindle pattern;
3. fibromatosis-like pattern.

Immunoprofiling helps to establish the diagnosis of IMT, with the identification of myofibroblasts, and with 50% of IMTs being ALK-positive [3]. Recently the relationship between IgG4 related disease (multi-organ system disease) and IMT has gained attention, with the possibility of overlap of the two conditions, as highlighted in this case [9]. Diagnosing IgG4 related disease is however challenging and even though biopsy is the gold standard investigation, samples are often inconclusive which creates the need for multiples procedures. Serological and histological findings can often be heterogenous which creates additional diagnostic pitfall [10].

A current literature search does not reveal any previous reported cases of IMTs of the submandibular gland. However, there are 5 international cases in the literature referring to "inflammatory pseudotumours" in the submandibular gland, a term which has now been superseded by the diagnosis of IMTs [11-15]. Management in these cases has largely focused on surgical resection. Inui et al. report an asymptomatic submandibular swelling in a 63-year-old male which resembled a malignant tumour radiologically that was treated with resection [16]. There was no recurrence reported after a 2.5 years follow-up. Similarly, Monteil et al. discuss a 58-year-old male presenting with a right submandibular swelling that was treated with surgical resection [12]. Firat et al. cast doubt on the use of chemotherapy in the treatment of IMTs and highlight the necessity of complete surgical resection [17]. They present a 55-year-old female diagnosed with a retroperitoneal IMT which required full resection after 2 cycles of chemotherapy and 2 previous unsuccessful partial surgical resections. No recurrence was reported after 7 months.

Steroids have also been used in the management of inflammatory pseudotumors. One case presents a 29-year-old female in India with submandibular swelling, anaemia and recurrent fever which was treated initially with steroids [4]. This patient subsequently developed abdominal pain with recurrent submandibular swelling and was diagnosed with abdominal tuberculosis. Her symptoms improved with steroids, antibiotics and Isoniazid prophylaxis. A second case report from India discusses a 20-year-old female with a 5-month history of left submandibular swelling which also responded well to steroids with the patient becoming asymptomatic within 5 months [11]. Additionally, conservative management of submandibular inflammatory pseudotumors has been reported in a 72-year-old male with poor general health [18]. The swelling in this patient reduced greatly over the following months. No evidence of recurrence was reported after a 2 years follow-up.

Prognosis for submandibular gland IMTs is not known due to its rarity but there has been reported a recurrence rate of 10-20% of head and neck IMTs. 28 patients with head and neck IMTs were studied in a 5-year retrospective study [19]. Maxillary IMTs were the most popular group in this study (6 patients). One patient studied had a submandibular IMT but little about this patient was discussed. 93% had wide surgical excision with all of these patients receiving corticosteroids prior to surgery. 39% received adjuvant radiotherapy. In total, 6 deaths were reported amongst this study group with 4 being IMT-related. 3 deaths related to local relapses and one was the result of sarcoma-transformation [19]. It is therefore apparent that the management of the patient presented in this case report is consistent with that of IMTs from other head and neck regions. The treatment of IMTs in head and neck remains unclear. Surgery is the main stay of treatment. High dose steroids have been used with some success. Invasive IMTs will usually undergo post-operative radiotherapy, and the ALK molecular-targeted therapeutic drug crizotinib has recently been trialled in some limited success [20].

Conclusion

IMTs are rare, usually benign, tumours showing variable clinical and radiological features. Case reports within the submandibular gland are very sparse. IMTs are a diagnostic challenge and only histological features can confirm their diagnosis. Classical features include fascicles of spindle cells in an inflammatory cell background and ALK positivity. There is no clear evidence on the treatment of IMTs. Literature suggests surgical resection is the most common method of managing these tumours along with the use of radiotherapy and corticosteroids. There is a risk of recurrence and the patients require long term follow up.

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