Review Article
Inflammatory myofibroblastic tumors of the head and nec

Jiang Tao[1,2], Min-Li Zhou[1], Shui-Hong Zhou[1]

[1]Department of Otolaryngology, First Affiliated Hospital, College of Medicine, Zhejiang University, 310003, China; [2]Department of Otolaryngology, Yinzhou People's Hospital of Ningbo City, Zhejiang Province, China

Abstract: Inflammatory myofibroblastic tumors (IMT) rarely affect the head and neck region. IMTs of the head and neck regions account for 14-18% of extra-pulmonary IMTs. Most commonly, they are located in the region of the orbits and upper airways, and less often at other sites. In the present study, we reviewed the English-language literature regarding the etiology, clinical features, diagnosis, treatment, and prognosis of IMTs of the head and neck.

Keywords: Inflammatory myofibroblastic tumors, head and neck, treatment, prognosis

Introduction

Inflammatory myofibroblastic tumors (IMT) are uncommon lesions [1]. Although they occur primarily in the lung, they have been reported to occur in various tissues and organs [1-3]. Variation in histologic appearance has led to a confusing nomenclature: inflammatory pseudotumors, plasma cell granuloma, atypical fibromyxoid tumors, myofibroblastic tumors, pseudosarcomatous tumors, inflammatory myofibrohistiocytic proliferation, myxoid hamartoma, lymphoid hamartoma, fibrous xanthoma, xanthomatous pseudotumors, fibrous histiocytoma, histiocytoma, mast cell tumors or mast cell granuloma, plasma cell pseudotumors and pseudosarcomatous lesions are synonyms that have been used to describe the same group of lesions characterized by chronic non-specific inflammatory changes [4, 5]. During the latter half of the 20th century, a debate occurred regarding whether IMTs were pseudo-tumors or neoplasms and whether they were benign or malignant [6, 7]. The concept of IMTs as neoplasms was established with the discovery of cytogenetic aberrations and the subsequent recognition of anaplastic lymphoma tyrosine kinase (ALK) gene rearrangements as a recurrent aberration in IMTs [3]. The world Health Organization (WHO) classification currently defines an IMT as an intermediate soft-tissue tumor comprising spindle cells that exhibit myofibroblast differentiation and numerous inflammatory cells, plasma cells, and/or lymphocytes [8]. Presently, some researchers have suggested that IMTs should be distinguished from the above synonyms under the umbrella term "inflammatory pseudotumors (IPTs)" [9, 10]. Gleason et al. suggested that IPTs should be only designated in IPTs of the lymph node, spleen and orbit.

Thus, an IMT is a biologically controversial entity, but most patients with an IMT have good prognoses and can be cured by resection [9]. IMTs may also occur as constitutional manifestations in a few patients, and they may have a multi-center presentation, locally aggressive growth and the capacity for vascular invasion [6]. In addition, they may recur locally and undergo malignant transformation in a few cases [6, 9-12].

IMTs rarely affect the head and neck region [1, 2, 4, 5, 7, 10-13]. IMTs of the head and neck regions account for 14-18% of extra-pulmonary IMTs [1, 6]. Most commonly, they are located in the region of the orbits and upper airways, and less often at other sites [4, 5]. In the present study, we reviewed the English-language literature regarding the etiology, clinical features, diagnosis, treatment, and prognosis of IMTs of the head and neck.

Etiology and pathogenesis

The etiology and pathogenesis of IMTs remain unclear. With the discovery of cytogenetic aberrations and subsequent recognition of ALK gene rearrangements, the hypothesis of an inflammatory origin was refuted by some researchers [6]. IMTs may arise as an immunologic host reaction to stimuli such as microorganisms, tissue damage, foreign bodies or neoplastic tissues [5].

ALK gene rearrangement

Almost 50% of IMTs occur via ALK gene rearrangements, which are located on chromosome 2p23. Immunohistochemically, approximately 50% of IMTs are positive for ALK [3]. The ALK gene may fuse with the clathrin heavy chain, tropomysin 3 (TPM3-ALK) or tropomyosin 4 (TPM4-ALK) [16]. Dysregulation of the ALK gene was correlated with tumorigenesis by promoting abnormal phosphorylation [1]. However, ALK gene abnormality is not the main cause of adult sinonasal IMTs [5]. Lazaridou et al reviewed the literature and found that ALK expression was not positive for sinonasal IMTs. In their 25-case series, only one patient showed ALK-1 positivity [5].

Viruses

The most studied viruses are Epstein-Barr virus (EBV) and human herpes virus-8 (HHV-8), and the results are controversial. IPTs have always been found to be positive for EBV and HHV-8 [17-23], primarily in the spleen and liver. According to Gleason et al., IPTs of the spleen and liver did not belong to the IMT scope [9]. However, Völker et al detected EBV by in situ hybridization and HHV-8 by immunohistochemical staining in two laryngeal IMTs, and no positive results were obtained [16]. Graefe et al. also showed EBV negativity for a case of IPT of the hypopharynx [24]. Additionally, EBV negativity was detected by polymerase chain reaction in a case of laryngeal IMT [25].

IgG4-related disease

Recently, the relationship between IgG4-related disease (IgG4-RD) and IPT/IMT has increasingly gained attention [26-36]. IgG4-RD is a multiorgan system disease that has been recognized in the last 10 years [26]. IMTs at some sites, such as the heart [27], central nervous system [28], ureter [29] and spleen [30], have been found to infiltrate IgG4-positive plasma cells, suggesting a possible overlap of IMTs with IgG4-related disease. In the head and neck region, some IPTs are characterized by the presence of numerous IgG4+ plasma cells [26]. Additionally, Segawa et al reported two cases of IPT arising from the head and neck region. One occurred at the orbit, and the other occurred at the parapharyngeal space. Immunohistochemically, the number of IgG4-positive cells was less than 40% of the number of IgG-positive cells, and the myofibroblastic cells were negative for anaplastic lymphoma kinase [36].

Trauma, chronic inflammation and autoimmune process

As Do et al. reported, several other common factors predispose to IMTs, such as trauma, smoking, and immune responses [37]. Additionally, Yan and colleagues hypothesized that the etiology of IMTs may be an uncontrolled response to tissue damage, chronic inflammation, or autoimmune process, and the probable inciting injury would seem to be related to the infection or injury with histoplasmosis [38]. Trauma and postinflammatory responses have been postulated as causes, and an association between trauma and IMT that may lead to reactive inflammation has been suggested [15]. As Biron et al. reported, an association is emerging between laryngeal trauma and pseudotumors; although causation cannot be proven completely, this connection has also been suggested as a predisposing factor for extralaryngeal pseudotumors [25].

Clinical features

Patients with an IMT generally present with non-specific symptoms and a mass, similar to that for malignant tumors. The mass then grows and oppresses the surrounding tissues, increasing the likelihood of local corresponding symptoms that are accompanied by pain, fever and weight loss. Anemia and the accelerated erythrocyte sedimentation rate (ESR) could also be found in laboratory examinations. IMTs of the head and neck present different clinical manifestations according to their different locations.

Nasal cavity-paranasal sinus IMT

Patients with a nasal cavity-paranasal sinus IMT present with non-specific symptoms,

including nasal obstruction, hemorrhinia and a mass that may grow slowly for several months or several years [39, 40]. Other specific symptoms could occur if IMT invades the surrounding tissues. Endoscopy usually identifies a polypoid mass or swelling mucosa, and bone destruction may be found in some patients. Additionally, imaging findings are non-specific. Maxillary sinus IMTs could present with bone destruction or invasive changes of the surrounding tissues, with mild-to-moderate reinforcement [41]. Computed tomography (CT) and magnetic resonance imaging (MRI) help to define the extent of the lesions and invasive changes of the surrounding tissues, contributing to the surgical outcomes.

Pharyngeal IMTs

Luo et al. reported six cases of tonsillar IMT [42]. These cases comprise two males and four females, and the mean age was 43 years (10-63 years). Clinical symptoms included laryngeal pain, odynophagia, pain in the neck, cough and dyspnea. The proportional morbidity ratio of the left side to the right side was four to two. CT found enlarged tonsils [42, 43]. To our knowledge, only one published case of pharyngeal IMT exists in the English language literatures concerning a 40-year-old male [24]. His main symptoms were weight loss and foreign-body sensation in the pharynx, and CT demonstrated a tuberculate mass.

Laryngeal IMT

IMTs of the larynx are rare benign lesions, and there are only 31 published cases of laryngeal IMT in the English language literature as reported by Alhumaid et al. [44]. Among these patients, males were the predominant gender, and the proportion of children was 22.5%. The onset age ranged from 19 months to 74 years. The most common pathogenetic site was the glottis portion, followed by the subglottis portion; the supraglottic portion was rare. The common symptoms were sound change (74%), stridor (29%), dyspnea and shortness of breath (22.5%), and foreign-body sensation (16%). Physical examination revealed a smooth-faced polypoid mass [45, 46]. Reports concerning the imageological examination of laryngeal IMTs are quite rare [47]. CT identified a soft-tissue mass [46] without enlargement of the cervical lymph nodes [45, 48], and contrast-enhanced CT revealed enhancement [46, 47],

while MRI showed a combination of high and low signals in T2-weighted imaging [47].

IMT of other parts of the head and neck

IMTs of the parotid gland are rare [49], and ultrasonography found no significant differences among other types of tumors. The morbidity of IMTs of other parts of the head and neck, such as soft tissues, the infratemporal fossa, the nasopharynx and the parapharyngeal space, is low [50].

Pathological features

Postoperative IMT specimens have been described as isolated or multinodular masses of uneven sizes, white or brown, with a ductile character. Some tumors may have different shapes. The sections of tumors manifest as heliciform, sarcoidosis or mucoid, with hemorrhage, necrosis or calcification. Some tumors manifest with an obloid center and a pink or red surrounding zone.

Histological manifestations of IMTs under the microscope are very complex and varied. IMTs have large amounts of cellular constituents, of which the main components are myofibroblasts and inflammatory cells. Myofibroblasts are arranged in a weaving shape or funicular shape, with acidophilus-stained cytoplasm and rounded or elliptic cell nuclei. Inflammatory cells include lymphocytes, plasmocytes, eosinophils, and macrophagocytes. Thus, the histological classification of IMTs is not unified. As Fujii et al. reported [51], IMTs could be divided into the lymphocyte type, granulomatous type and sclerosing type according to their histological features, but most researchers do not agree with this view. Coffin et al. analyzed the pathological characteristics of 84 clinical cases of extrapulmonary IMT [6], and three basic histologic patterns were recognized: (a) myxoid, vascular, and inflammatory areas resembling nodular fasciitis; (b) compact spindle cells with intermingled inflammatory cells (lymphocytes, plasma cells, and eosinophils) resembling fibrous histiocytoma; and (c) dense plate-like collagen resembling a desmoid or scar. These three patterns could overlap, or priority is given to (a) or (b), and this pathological classification method is universally accepted presently.

The morphology of fibrocytes is concerned with the cell cycle, and their morphologies differ

according to cell cycle stage. Electron microscopy revealed that IMTs contain myofibroblasts, inflammatory cells (plasmocytes and macrophagocytes) and blood vessels rich in endothelial cells and well-differentiated fusiform myofibroblasts [52]. IMT cells contain abundant myofilaments, developmental rough endoplasmic reticulum and a well-differentiated Golgi complex. The cytoplasm of IMT cells contains thin myofilaments and thick zones, while the cytomembrane contains secretory vesicles of collagen particles, and fibrous joints, desmosome structures and lysosomes are evident [53, 54].

Immunohistochemical staining is applied for the phenotypic detection of myofibroblasts, and could contribute to the diagnosis and differential diagnosis. However, other components of cells showed positive expression of muscle-specific actin (MSA), smooth muscle actin (SMA), desmin (DES) and vimentin [52]. Other positive expressers include CD34, CK and S-100. Generally, IMTs have three phenotypes: (a) only positive vimentin expression; (b) positive expression of myogenic proteins such as DES, SMA and MSA; and (c) positive expression of CK. Vimentin expression is usually positive, but it has low specificity. SMA positive expression is a very important marker, and positive expression of ALK1 could contribute to the diagnosis of IMTs [55]. Clinical features of IMTs are non-specific, and their diagnosis requires pathological examination. Immunohistochemical staining is important for the diagnosis and differential diagnosis of IMTs.

Treatment

The treatment of IMTs of the head and neck remains unclear; currently, the main therapy is empirical therapy. Surgery is the main therapy of IMTs of the head and neck. Postoperative large-dose hormone therapy of the whole body is administered when the tumor cannot be completely resected, or the surgical margins are positive; the hormone therapy should last for several years. Some patients require therapy with the combination of hormones and surgery. Invasive IMTs require radiotherapy, and the ALK molecular-targeted therapeutic drug crizotinib has been applied in some patients [56]. A controversy exists concerning the treatment of nasal cavity-paranasal sinus IMTs. Some researchers prefer a large dose of hormone therapy, while others choose surgery.

Early lesions of IMTs have a good response to hormone therapy, while later lesions are not sensitive; radiotherapy is applied in few patients [40]. The main therapy of tonsillar IMTs is tonsillectomy, and it can be supplemented by CO_2 laser light [42]. The main therapy of laryngeal IMTs is complete removal of the tumor, with supplementation by CO_2 laser light and postoperative hormone therapy [44, 47]. Recurrent patients could choose hemilaryngectomy, while chemoradiotherapy is suitable for only a few patients with cancerization [47]. Most researchers state that the main therapy of pediatric IMTs of the head and neck should be resection, and there is no need to perform chemoradiotherapy after surgery. Instead, hormone therapy should be performed routinely in pediatric IMTs of the head and neck [57].

Prognosis

As Meis et al. reported, of the patients with a mesenteric IMT or a retroperitoneal IMT, 37% showed recurrence, 11% had distant metastases, and 18% died [58]. The locoregional recurrence rate of IMTs of the head and neck is ~10-20% [56]. Cytometaplasia, genetic recombination, cancerization and metastasis could occur in IMT patients. The prognosis of IMTs is connected to the surgical margin, tumor size, ALK level and the condition of necrosis [1, 56].

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shui-Hong Zhou, Department of Otolaryngology, The First Affiliated Hospital, College of Medicine, Zhejiang University, 310-003, China. Tel: 86-571-87236894; Fax: 86-571-87236895; E-mail: zhouyunzhoush@163.com

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