Clinical Pathologic Conference Case 3: Nodular Fasciitis

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Abstract Intraoral nodular nodular fasciitis is a rare entity that is important to recognize because it may simulate a malignancy clinically and histologically. The rapid growth and high mitotic index seen in nodular fasciitis may suggest a malignant neoplastic process, but it is generally considered to be a benign reactive proliferation. Recognizing the unique histologic features of nodular fasciitis is important to avoid a possible misdiagnosis as a malignancy, leading to unnecessary further treatment.

Keywords Nodular fasciitis · Oral cavity · Soft tissue tumors

Clinical Presentation

An asymptomatic 28-year-old male complained of a rapidly enlarging pedunculated swelling of the left mandibular vestibule, which he first noticed 2–3 weeks prior to clinical examination (Fig. 1). He reported no bleeding and denied a history of trauma. Panoramic radiographic examination confirmed the peripheral origin of the lesion by ruling out involvement of the underlying mandibular bone.

Differential Diagnosis

The clinical differential diagnosis for a young male presenting with an ulcerated, pedunculated mass of the mandibular vestibule includes various reactive and neoplastic lesions. Given the rapid onset of this patient's swelling and the marked ulceration, benign lesions were deemed less likely than their malignant counterparts. Neither infections nor developmental conditions were seriously entertained as likely diagnoses.

Among reactive proliferations, pyogenic granuloma was considered likely, although these show a female predilection and tend to develop more often on the attached gingiva rather than in the vestibule. Nodular fasciitis is a myofibroblastic proliferation originally described as pseudosarcomatous due to its tendency to grow rapidly and display cytologic atypia. The peak incidence is in adulthood and although the etiology is unknown, it is believed to be due to trauma. Although oral lesions are rare, several cases have been reported, most commonly on the buccal mucosa [1]. Inflammatory myofibroblastic tumors (originally described as “pseudotumors”) are another reactive proliferation known for rapid growth. Oral lesions most commonly involve the maxillary sinus, buccal mucosa, or gingiva [2].

Numerous soft tissue sarcomas may also be reasonably entertained as diagnoses. These include tumors of fibrous, vascular, lipomatous, neural, and muscle differentiation. Leiomyosarcomas are smooth muscle malignancies that infrequently present in the oral cavity. Most patients present in the 4th decade (median age, 37) with a painless mass involving the jawbones [3]. These tend to be associated with aggressive clinical behavior and poor survival. Oral rhabdomyosarcomas also may present as rapidly enlarging painless masses. There is a predilection for the

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Fig. 1 Clinical examination revealed an ulcerated and pedunculated soft tissue swelling of the *left* mandibular vestibule

head and neck region, with the soft palate as the most common intra-oral site [4].

Hematologic malignancies were also considered in the differential for this lesion and included myeloid sarcomas, non-Hodgkin lymphomas, and multiple myeloma. Myeloid sarcomas, formerly known as granulocytic sarcomas or chloromas, are solitary masses of myeloblasts in extra-medullary sites; 40% appear in the head and neck region; although the tumor is associated with acute myeloid leukemia, it may also present on the gingiva in patients with no known history of a hematologic malignancy [5]. Clinical signs of oral non-Hodgkin lymphoma commonly include swelling, ulceration, and destruction of bone. Although the vestibule is the fourth most common oral location, patients are significantly older (mean age, 71), unlike the patient in this case [6]. Multiple myeloma is a malignancy that may present with plasma cell proliferations in the oral soft tissues; this tends to be a diagnosis of older individuals (between ages 50 and 80), rarely diagnosed prior to age 40 [7].

Although the the mandibular vestibule is not classically considered a high-risk location for squamous cell carcinoma, any discussion of oral cancer would be incomplete without mention of this most common form of oral cancer. When seen in patients younger than age 40, 11% of lesions present on the alveolus and gingiva [8]. The sarcomatoid variant of squamous cell carcinoma, which has a spindle cell morphology, was considered since this type frequently presents as a pedunculated mass, as seen in this case.

Other forms of cancer deemed unlikely due to the patient's young age and the anatomic location include malignant mucosal melanoma and metastasis. Oral melanoma is rare, accounting for less than 8% of all melanomas and is seldom seen in patients younger than age 30. When encountered, oral melanoma occurs most often on the maxillary gingiva or hard palate and may present as an

ulcerated and painless mass [9]. Metastasis to the oral cavity tends to spread most often to the jawbones; less often, the soft tissues of the gingiva may be involved [10]. The most common primary tumors that metastasize are carcinomas that tend to affect older individuals, rendering this diagnosis less likely.

Diagnosis and Discussion

The patient underwent an excisional biopsy of the soft tissue mass. The surgeon encountered a well-defined mass that had smooth borders and submitted the specimen, humorously, with a clinical diagnosis of a “Texas-sized” pyogenic granuloma. The gross specimen consisted of a 2.0×2.5 cm soft tissue mass that was firm and slightly gelatinous in consistency (Fig. 2).

Histopathologic examination of hematoxylin and eosin stained sections revealed a largely ulcerated lesion composed of a proliferation of spindle cells organized in a fascicular pattern that was loose and “feathery,” resembling cells growing in tissue culture (Fig. 3). Some areas of the tumor exhibited myxoid degeneration while other areas were more fibrotic and hyalinized with evidence of adjacent microhemorrhage and granulation tissue. The periphery of the lesion was well-defined, but no fibrous capsule was apparent. The incorporation of adjacent skeletal muscle bundles was seen at the periphery (Fig. 4). A mixed inflammatory cell infiltrate was present throughout the lesion. On higher magnification, the proliferating cells appeared to have ovoid pale-staining nuclei with prominent nucleoli (Fig. 5). The cells were mitotically active but nuclear pleomorphism was not apparent. Cytomorphologically, the cells resembled fibroblasts or myofibroblasts.

Fig. 2 The gross specimen measured slightly greater than 2.0 cm in length

Fig. 3 A “tissue culture”- like proliferation of spindle cells is exhibited (Hematoxylin and eosin stain. Original magnification 20X)

Fig. 4 The periphery of the lesion incorporates individual skeletal muscle fibers (Hematoxylin and eosin stain. Original magnification 10×)

Fig. 5 Ovoid pale-staining nuclei and numerous mitotic figures are seen (Hematoxylin and eosin stain. Original magnification 40×)

Fig. 6 Smooth muscle actin stain demonstrates strong intracytoplasmic positivity (Smooth muscle actin stain. Original magnification 20×)

Based on the histologic features, a provisional diagnosis of nodular fasciitis was rendered. Further immunohistochemical studies were ordered to confirm the nature of the proliferating spindle cells. The lesional cells of nodular fasciitis are known to be myofibroblasts, which stain positively with smooth muscle actin and muscle specific actin [11]. Desmin is rarely expressed, β -catenin is characteristically not expressed and some authors have described positive staining with CD68 [11, 12]. In this case, strong positive intracytoplasmic staining was seen with smooth muscle actin throughout the lesion, and a definitive diagnosis of nodular fasciitis was finalized (Fig. 6).

Nodular fasciitis usually presents as a single nodule 5 cm or less in size. It may occur as multiple nodules in one area, but usually does not affect multiple anatomic sites concurrently.

Adults between the ages of 20 and 40 are most commonly affected [13]. The skin of the upper extremities is the most common location, followed by the trunk, and the head and neck. In infants and children, the head and neck are the most common sites affected. Nodular fasciitis has been reported in the facial skin around the nose and infraorbital area, angle of the mandible and submental area. Intraorally, it can occur in the vestibule, labial and buccal mucosa, mandibular alveolar ridge, or tongue [13]. Grossly, nodular fasciitis may be soft and gelatinous in consistency, similar to a myxoma or a benign peripheral nerve sheath tumor. When more collagenous and firm, it may resemble fibromatosis, a locally recurring, non-metastasizing proliferation of fibrous tissue [13].

Although the cause of nodular fasciitis is unknown, it is speculated to be a reactive myofibroblastic proliferation initiated by local trauma [13]. The histologic resemblance to organizing granulation tissue supports this theory of its

origin. However, there is some evidence from cytogenetic analyses that nodular fasciitis might be a clonal proliferation [14]. The term “fasciitis” implies that it is an inflammatory lesion originating in the fascial connective tissue surrounding blood vessels, nerves, and muscle. Intraoral nodular fasciitis is extremely rare, perhaps because fascia is not as prominent in the oral cavity as at other anatomic sites [15]. In a review of 36 cases of intraoral nodular fasciitis, buccal mucosa and tongue were the most commonly affected sites [1]. This supports the theory that it is a reactive proliferation, since these are easily traumatized areas.

This case is characteristic of many cases that present as rapidly growing masses present for 1–2 weeks. In approximately half of all cases, patients complain of soreness, tenderness, or slight pain [13]. Acute, severe pain or paresthesia are rare, but may occasionally occur when the rapidly growing nodule puts pressure on an adjacent peripheral nerve. Nodular fasciitis was first described by Konwaler in 1955 as a “subcutaneous pseudosarcomatous fibromatosis [16].” Because of its rapid growth, cellularity, and active mitotic rate, Weiss and Goldblum call it the most common benign mesenchymal lesion that is misdiagnosed as a sarcoma [13].

Histologically, the differential diagnosis may include proliferative fasciitis, which is considered a variant of nodular fasciitis, and can also contain tissue culture -like fibroblasts and myofibroblasts in a myxoid or collagenous background stroma. It also grows rapidly and a history of trauma is reported in approximately one-third of cases [17]. In contrast with nodular fasciitis, it tends to be poorly circumscribed and often contains large, polygonal “ganglion-like” cells, and it affects a slightly older population (age 40–70) [17]. A number of benign neoplasms can have histologic features resembling nodular fasciitis. Myxoma, myofibroma, fibrous histiocytoma, and fibromatosis can be differentiated from nodular fasciitis by their growth pattern and cytologic features. Fibromatosis can further be distinguished by the positive expression of β -catenin, which is not expressed in nodular fasciitis [12]. Inflammatory myofibroblastic tumor would contain a much more prominent inflammatory cell infiltrate and is characterized by ALK gene rearrangement, which is not seen in nodular fasciitis [18].

A few malignant neoplasms can share histologic features with nodular fasciitis. Fibrosarcoma can also have an active mitotic rate, but would be characterized by atypical mitoses and significant nuclear pleomorphism. It can additionally be differentiated by its growth pattern and cellularity [13]. Characterized by densely packed interweaving bundles of spindle cells forming a “herringbone pattern,” fibrosarcoma typically occurs in a deeper location, is larger in size, and has a longer duration. Other

spindle cell malignancies which might be included in the histologic differential diagnosis are monophasic synovial sarcoma, leiomyosarcoma, and malignant peripheral nerve sheath tumor.

Nodular fasciitis rarely recurs after conservative surgical excision is performed. The case we are reporting showed no recurrence at follow up 1 year after local excision. In a large series of 895 cases of nodular fasciitis, only 1% of cases recurred [19]. This case demonstrates the importance of including this unique entity in the differential diagnosis of a rapidly-growing ulcerated lesion. Because it can simulate a malignancy both clinically and histologically, awareness and familiarity with this benign proliferative lesion can prevent a possible misdiagnosis of malignancy, resulting in unnecessary treatment.

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