Fibromatosis of the Head and Neck: Morphological, Immunohistochemical and Clinical Features

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Abstract. *The term fibromatosis indicates a proliferation of well-differentiated fibroblasts and myofibroblasts that develops in the soft tissue. This tumor has been considered locally aggressive because of the infiltrative growth pattern, but does not metastasize. Its occurrence in the head and neck region is not common, and very sporadically it may occur in the oral cavity or jaw bones. Two cases of adult fibromatosis are described here; one involving the submucosa of the middle hard palate and the other the subcutaneous area of the frontal bone. Tumor growth was rapid and bone involvement occurred in one case. Biopsies were taken and in both cases histological examination showed a tumor consisting of fibroblasts within a collagenous stroma, with rare atypia and mitoses. The patients underwent surgical resection with wide surgical margins; excised material was analyzed microscopically and a diagnosis of fibromatosis was rendered. Immunohistochemistry was positive for actin, vimentin and desmin, and negative for S-100, CD34, the progesterone receptors (PR)-A and PR-B and the estrogen receptors (ER)α and ERβ. Follow-up at 5 years after surgery found both patients to be progression free. The clinical, histological and immunohistochemical features were analyzed to better characterize this form of the disease, that very rarely involves the oral cavity.*

The classification of fibromatosis has not yet been standardized, and some forms derive their names from their particular locations. The terminology of the WHO classification was employed, using the term extra-abdominal fibromatosis, however, other terms exist, including extra-abdominal desmoid tumor, desmoid tumor, well-differentiated non-metastasizing fibrosarcoma, grade I fibrosarcoma and aggressive fibromatosis. The latter term emphasizes the clinical nature of the disease process, indicating the aggressive behavior it may sometimes show. The lesion usually arises from the connective tissue of the muscle, the overlying fascia or aponeurosis and two principal forms are recognized: juvenile fibromatosis and adult fibromatosis.

Adult extra-abdominal fibromatosis is an uncommon soft-tissue tumor that can occur at any anatomic site, the commonest being the limbs, shoulder, thigh, buttock and trunk (1, 2) and accounts for 6.9% of all soft-tissue tumors (3). Occurrence in the head and neck region is not common (5-10%) (3-5) and only sporadically does it occur in the oral cavity or maxillary bones. Clinically, in the oral cavity it usually presents as a painless mass or swelling in the region involved. Less commonly, the patient shows ulceration, trismus, intraoral bleeding, otalgia, disphagia, dyspnea, and loose teeth (6). The peak of incidence is between the ages of 25 and 35 (7), both genders being equally affected. The etiology of fibromatosis is still controversial. Genetic (7), endocrine (8, 9), and physical factors including surgery, trauma (10) and irradiation (11) may play roles in causing or precipitating fibromatosis, although Morioka *et al*. (12) found no evidence of trauma or familial predisposition in relation with the disease. A viral theory has also been proposed, but no virus has been isolated (13).

Macroscopically, fibromatosis traditionally appears as an ill-defined and firm grayish-white mass. Histologically, it is composed of well-differentiated fibroblasts, fibrocytes and myofibroblasts within a collagenous to myxoid stroma. No atypical mitosis or anaplastic elements are seen. However, it resembles a 'borderline' lesion, with an infiltrative growth pattern that makes complete excision difficult, and it has a propensity for recurrence, however, it does not metastasize. Diagnosis of this entity should include panoramic tomography, ultrasonography and MRI. CT and MRI show

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Key Words: Fibromatosis, desmoid tumor, oral cavity.

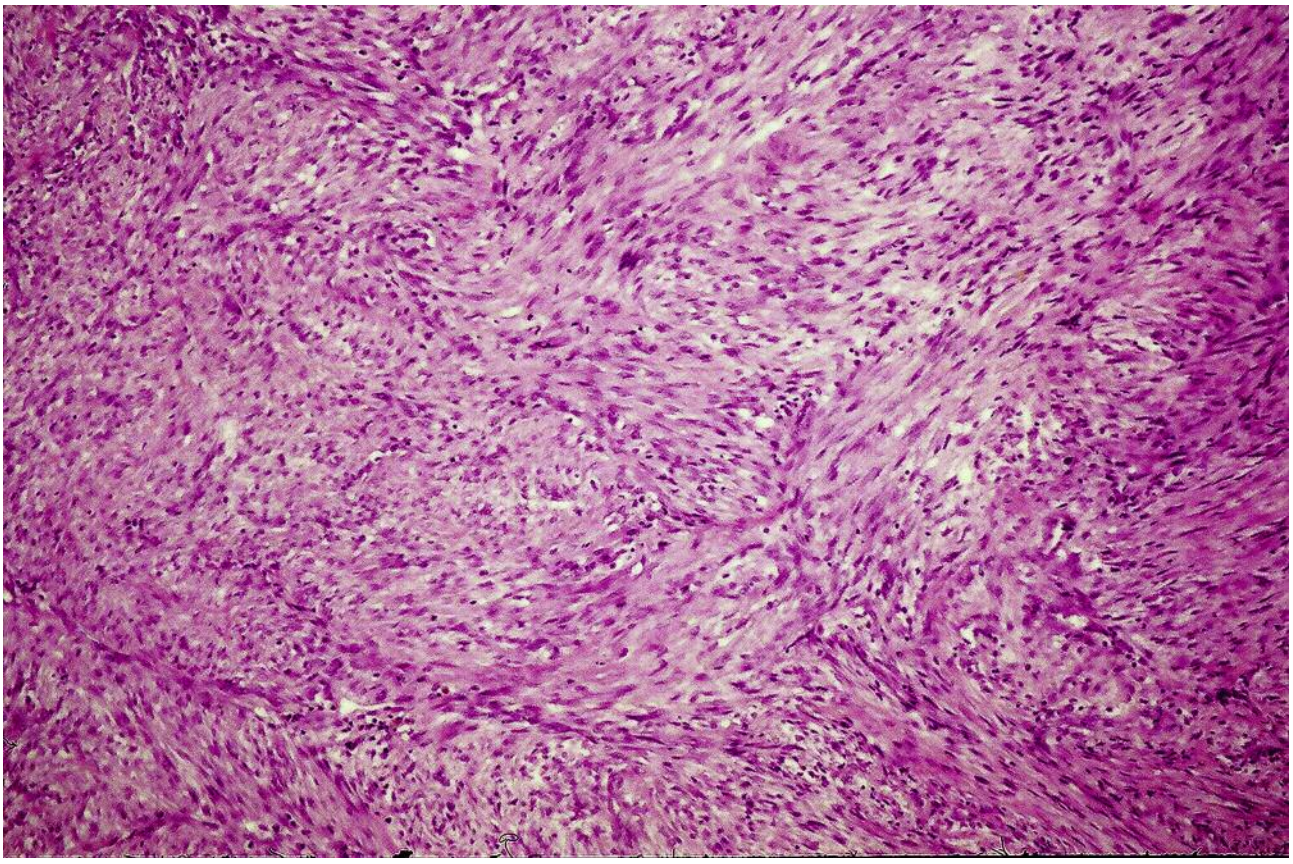

Figure 1. *Photomicrograph shows proliferation of spindle cells with bland nuclei and the fascicular arrangement (Hematoxylin and eosin; original magnification ×150).*

the extension of the lesion and any infiltration of the surrounding tissues and in planning surgical excision (13, 14). Fibromatosis may attain a large size and cause compression, infiltration, and destruction of adjacent structures. Such growth behavior presents severe management problems, especially in the head and neck region, where the presence of many vital structures within a small space makes the patient susceptible to the effects of the fibromatosis, likewise making complete excision difficult.

Two rare cases of fibromatosis are reported, one involving the frontal bone and the other the hard palate, diagnostic imaging is provided, the histological and immunohistochemical features are discussed, together with the therapeutic approach.

Case Reports

Case 1. A 39-year-old woman was admitted to our department with a one-year history of small growth in the center of the hard palate. Oral examination showed a growth in the hard palate that did not pulsate and was not painful on palpation. An incisional biopsy revealed a lesion consisting of fibroblasts with rare atypical aspects and mitotic activity. CT scanning revealed a soft-tissue mass around the mid-palate with predominately homogenous attenuation and mild enhancement. The tumor (a 2.0×2.5×2.0 cm grey-white lobulated mass) was excised with wide surgical margins. Recovery was uneventful and CT 5 years later showed no sign of recurrence.

Case 2. A 29-year-old man presented with a frontal mass that had been present for two years. CT scanning revealed a 2-cm mass extending superiorly to the frontal region, inferiorly to the orbital area. Family medical history was negative for neoplastic diseases. A general physical examination showed no abnormalities. An incisional biopsy revealed fibromatosis. The gray-white mass was then excised with wide surgical margins, the patient was followed-up and showed no signs of recurrence 5 years post-surgery.

Materials and Methods

The excised surgical specimens were fixed in 10% buffered-formalin and paraffin embedded, 5 μ sections were stained with

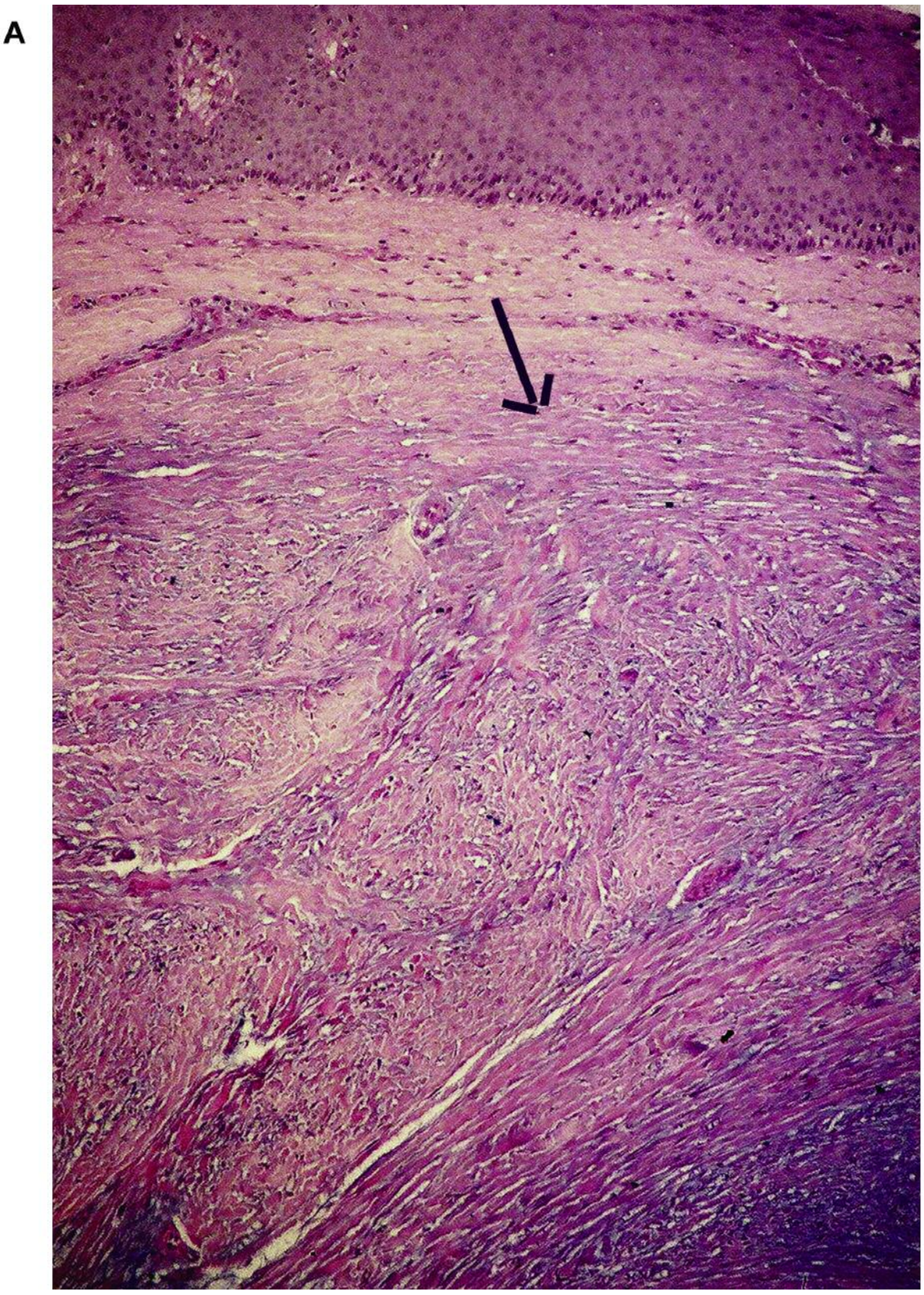

Figure 2. *continued*

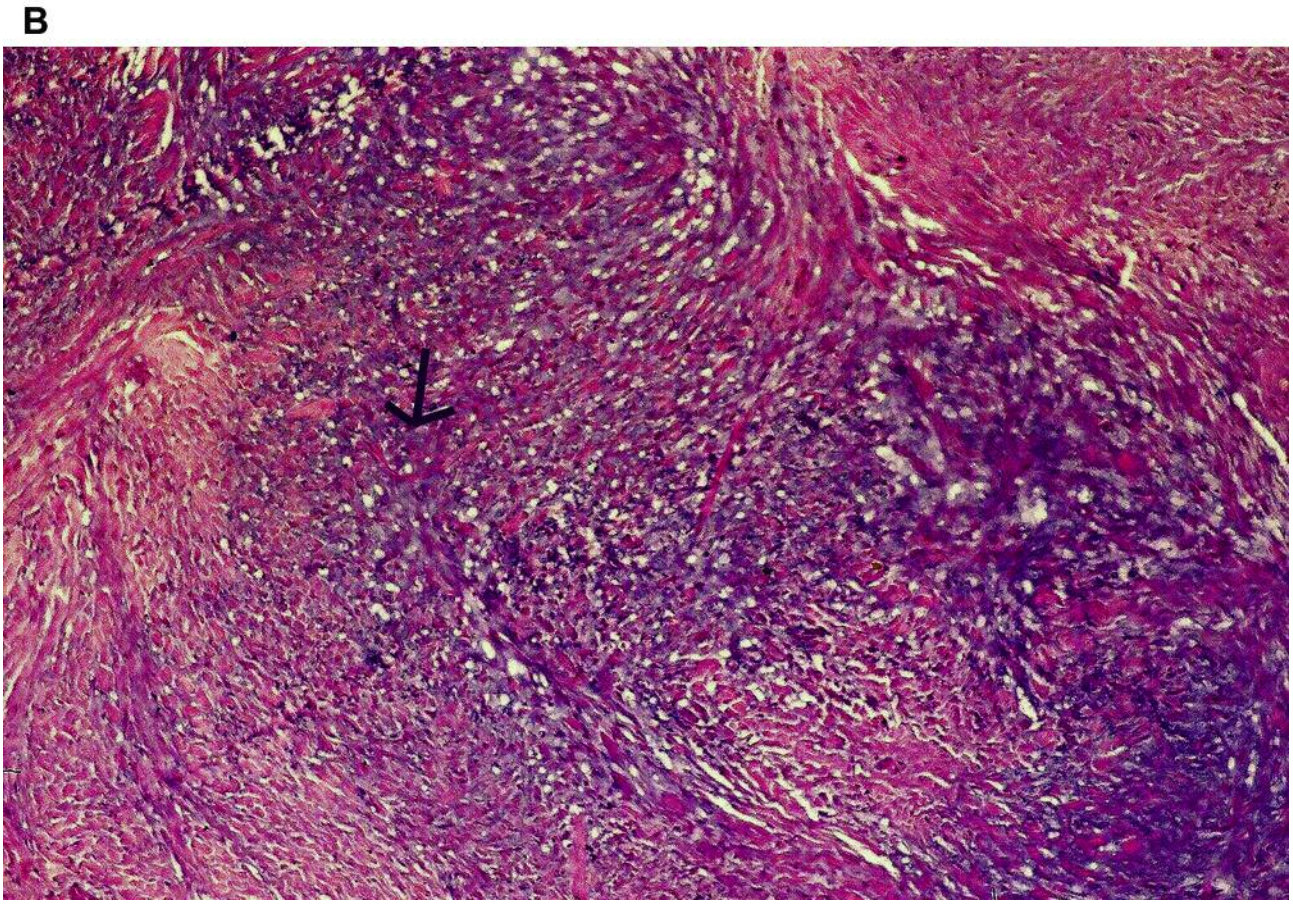

Figure 2. *A. Photomicrograph shows (arrow) the characteristic nodular growth pattern (Hematoxylin and eosin; original magnification ×100). B. Note the characteristic interlacing bundles of fibroblasts separated by collagen (arrow) (Hematoxylin and eosin stain; original magnification ×200).*

Table I. *Immunohistochemical findings of the current cases.*

Antibody	Supplier	Dilution	Reactivity case (1)	Reactivity case (2)	Antigen retrieval
Actin	Dako	1:100	+	+	Np
Desmin	Neomarkers	Prediluted	+	+	Citrate pH6
Pancytokeratin (A1-A3)	Ylem	1:50	–	–	Citrate
Ema	Dako	1:50	–	–	Np
S-100	Dako	Prediluted	–	–	Np
CD34	Ylem	Prediluted	–	–	Np
Oestrogen receptor α-β	Dako	1:100	–	–	Citrate pH6
Progesterone receptor A-B	Dako	1:400	–	–	Citrate pH6
Vimentin	Dako	1:400	+	+	Np

+: positive for a limited number of cells; Np: not performed.

hematoxylin-eosin, and with PAS (Periodic Acid-Schiff). For immunohistochemistry, the avidin-biotin complex (ABC) method was applied. All the tissue sections were dewaxed and rehydrated following standard protocols. Table I provides the details of the antibodies used. A panel of monoclonal antibodies was used for the following markers (Table I): actin (1:100, Dako), vimentin (1:400, Dako), desmin (Prediluted, Neomarkers), pancytokeratins (1:50, Ylem), EMA (Epithelial membrane antigen) (1:50, Dako), CD34 (prediluted, Ylem), S-100 (Kit Dako, prediluted), estrogen receptors (ER)α-β (1:100, Dako), and the progesterone receptor (PR) (1:400,

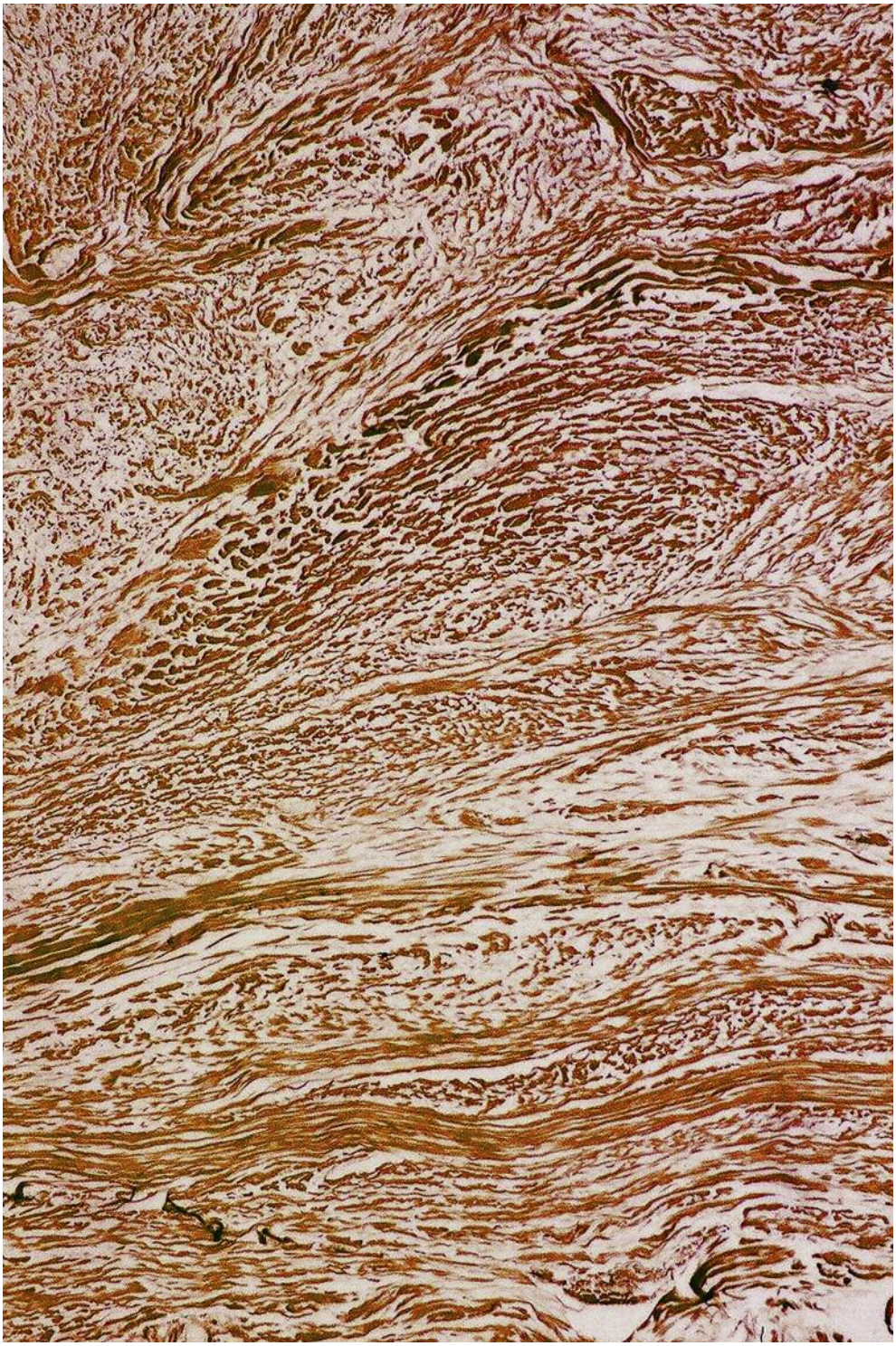

Figure 3. *Immunohistochemically the spindle cells in Case 1 showed strong reactivity for vimentin (original magnification ×200).*

Dako). The tissue sections were processed following the manufacturers' guidelines or standard protocols. All the slides were evaluated independently by light microscopy by two pathologists. Classification as positive either followed manufacturers' guidelines or institutional standard protocols for positive controls: a minimum of 10% of the tumor cells had to be positive for the ERα and β, and the PR-A and B. The immunohistochemical reactivity for EMA, S100, CD34, vimentin, desmin and actin, was evaluated and graded

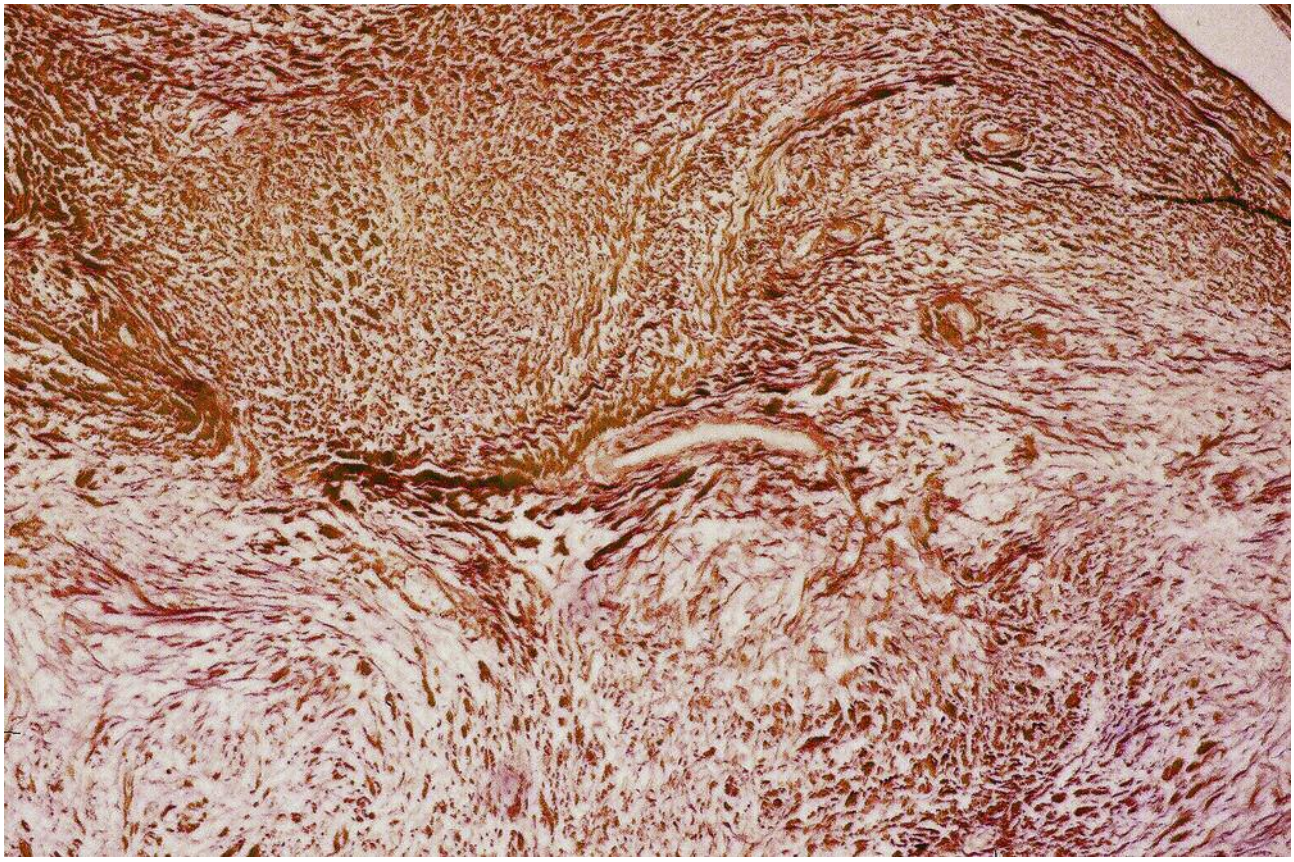

Figure 4. *Immunohistochemically in Case 2 strong reactivity for vimentin (original magnification ×200).*

as follows: – (negative), no staining; + (positive), focally positive for a limited number of cells and ++ (intensely positive), focally or diffusely positive for numerous cells.

Results

Microscopic examination in case 1 showed that, beneath the squamous epithelium, which was covered by a thin layer of anucleate corneous lamellae, the lesion was composed of some nodules of connective elements arranged in a vortex of interlacing bundles of fibroblasts separated by collagen, immersed in a mixed stroma, which was lightly basophilic and moderately alcian positive (Figure 1).

The histology showed in case 2 showed a nodule of fibrous tissue with poor cellularity, consisting of thin mature spindle-shaped fibrocytes, interspersed with islands of connective tissue containing capillaries, whose walls were delimited by enlarged and thickened endothelial cells mixed with small nerve branches, arranged irregularly. Along one side in the fibrous tissue there was an area of osteoid aspect, forming at its edges bone tissue of normal appearance (Figure 2A-B).

Table I shows the results of the immunohistochemical staining. Immunohistochemical reactivity for vimentin, actin, desmin, ERα-β, and PR A-B was detected.

Both cases were negative for EMA, S-100, CD34, cytokeratins, PR-A and PR-B, and for ERα and ERβ and positive for actin, vimentin and desmin (Table I and Figures 3 and 4).

Discussion

Biopsy was essential, because only histological examination can distinguish between the various forms, of the disease and above all it is important for differential diagnosis. Several diseases should be included in differential diagnosis since desmoplastic fibroma, the osseous counterpart of fibromatosis, presents a fairly similar appearance, but is less cellular and does not infiltrate as widely as fibromatosis. Clinical and radiological aspects also help in defining the lesion. Neurofibroma should also be considered in the differential diagnosis, but it is always S-100 positive, while fibromatosis is not, likewise malignant peripheral nerve-

sheath tumor, which is more cellular and presents greater mitotic activity, and in which about half of the cases are S-100 positive.

The most significant differential diagnosis is *versus* fibrosarcoma, which is diagnosed when the tumor cells show atypical cytological features and/or a significant number of mitotic figures (more than 1 per high-power microscopic field) (15). This differentiation may be difficult, but it is essential since fibromatosis does not possess the metastasizing potential of fibrosarcoma.

In cases located in the bone, there are problems of differential diagnosis *versus* the monostotic form of fibrous dysplasia (Jaffe Lichtenstein Syndrome), in which high activities of alkaline phosphatase are detectable. Other diseases must also be considered, such as Albright's syndrome, cherubism (in which however the age and presence of giant cells are indicative for diagnosis) or tumors such as neurofibroma (in which negativity for S100 is diagnostic) and also proliferative myositis (an intramuscular reactive process in which the hallmark is the ganglion-like cells, absent in fibromatosis). With regard to histopathology, no atypia was detected in the proliferating fibroblasts in our cases, and mitoses were also completely absent in one case and very rare in the other case.

Both of our cases were positive for actin, desmin and vimentin, but negative for pancytokeratin, EMA, S-100, CD34, PR-A, PR-B and ERα and Erβ. The sex hormones receptors were tested because fibromatosis in general is thought to be hormonally sensitive, and because young fertile women are often affected, and anti-estrogens have been used as adjuvant treatment, either successfully (16) or without benefit (17, 18).

The treatment of choice for fibromatosis is complete surgical resection with wide margins (9, 19). In head-and-neck cases the vital and complex anatomy of the area (5) and similarly the occurrence of fibromatosis in this area can lead to loss of function associated with the destruction of these vital structures. The recommended margins are 2 and 4 cm respectively in the transverse plane and along the longitudinal axis, and less than 3 cm in the case of small tumors (20). Thus, many patients with large fibromatosis of the head and neck region must be treated with non-surgical options, such as radiotherapy and chemotherapy. The use of adjuvant therapy remains controversial. External radiotherapy or interstitial brachytherapy have been recommended as a substitute for radical surgery to avoid severe disability when limbs are affected (*e.g.* amputation) (21-23) while other studies (20, 24) have failed to demonstrate the value of additional radiotherapy. Zelefsky *et al*. (22) reported good results with brachytherapy for recurrent fibromatosis after surgical resection and achieved local control in 70% of patients. Irradiation may play a role in inoperable cases. In some inoperable cases radiotherapy is preferred, and if radiotherapy is contraindicated, chemotherapy is a valid alternative (25). An experimental protocol based on a combination of three drugs (vincristine, actinomycin D and cyclophosphamide) can be used and must be combined with continuous follow-up with MRI. If the patient is estrogen-receptor positive, anti-estrogen drugs can be used with fairly satisfactory results. Alternatively, a combination of testolactone, sulindac, warfarin and vitamin Kl can be given (26).

Other therapies have been proposed, in particular with the availability of anti-estrogen drugs (tamoxifen), on the grounds that the speed of growth of fibromatosis is regulated especially by the female sex hormones (1, 27). However, the results of this type of treatment have not yet been fully clarified (1, 5, 10, 18, 21, 28).

Adult fibromatosis is characterized by a local recurrence rate of 35-65%. Hoos *et al*. (10) have reported a local recurrence rate in extra-abdominal desmoids of between 20-77%, 46-62% in the head and neck region, whereas Morioka *et al*. (12) reported a recurrence rate of 40-70%. Enzinger and Shiraki (24) report that younger patients and larger tumors have a higher propensity to recur. This behavior is slightly different in extraabdominal fibromatosis compared to the abdominal fibromatosis (desmoid tumor), in which the recurrence rate is lower (15-30%).

In summary although our series was small, the behavior of fibromatosis in the oral cavity does not appear to be very different from that of the systemic disease. Problems of differential diagnosis concern a wide range of other diseases and immunohistochemical analysis may be helpful in diagnosis. Our limited experience was characterized by a long follow-up period (5-6 years) and shows that in the management of head and neck fibromatosis a careful surgical excision with wide margins is of value for small lesions, to avoid possible recurrence.

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