In the literature reviewed, most of the case reports of ESFA are associated with reactive conditions; but in our patient, there apparently was no history of diabetes mellitus or any other reactive condition. Hence ESFA may probably arise as a benign neoplastic proliferation of acrosyringeal cells.

We followed our patient for 1 year and 3 months after surgery. There was no evidence of any recurrence. Every diagnosed case of ESFA should be followed in view of risk of developing carcinoma because there are some reports of cases of ESFA with carcinomatous transformation. [6]

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Matrix metalloproteinase-9 expression in a CD34-positive glomus tumor with myxoid stromal change

Sir,

Glomus tumors commonly present as solitary lesions and typically occur in the dermis or subcutis of extremities of the adults. Subungual region of the finger is the most common localization for these tumors. Microscopically, a glomus tumor has distinctive histological features. It is a well-demarcated or encapsulated dermal or subcutaneous lesion composed of sheets or nests of uniform glomus cells surrounding blood vessels. [1] Immunohistochemically, glomus tumor cells express vimentin, actin, and myosin, while desmin is generally negative. [2]

A 56-year-old woman was admitted with a complaint of a nodule located at the lateral side of the fifth finger of her right hand. The lesion was completely excised and submitted for histopathological examination. On gross pathology, a nodular encapsulated lesion measuring 8×5 mm was observed at the cut surface of the excised specimen. At histopathological examination, a well-demarcated tumoral lesion with a fibrous capsule was noted in the reticular dermis. Tumor tissue was composed of nests of rather uniform cells with acidophilic cytoplasm and round-to-oval nuclei and these nests were interrupted by blood vessels. Tumor cells surrounded the blood vessels in many areas. A prominent myxoid change was noted in the tumor stroma [Figure 1]. Tryptase immunohistochemistry (1/100, Neomarkers, Fremont CA) highlighted the mast cells scattered around. The number of mast cells was over 20 per high-power field (HPF). No diffuse cellular atypia or mitotic activity was noted within the tumor tissue. Immunohistochemically, smooth muscle actin (1/200, Neomarkers, Fremont CA) and CD34 (1/50, Neomarkers, Fremont, CA) were positive in all tumor cells [Figure 2]. Endothelial cells also showed diffuse staining for CD34. The histopathologic diagnosis was that of a CD34-positive glomus tumor with a myxoid stroma. Regarding the myxoid stromal change encountered in the present case, additional immunohistochemical staining was performed for matrix metalloproteinase-2 (MMP-2) (pre-diluted, Neomarkers, Fremont, CA) and matrix metalloproteinase-9 (MMP-9) (1/25, Neomarkers, Fremont, CA) in order to find out if they are expressed within the tumor tissue. MMP-9 immunohistochemistry showed a consistent but rather weak cytoplasmic staining in most of the tumor cells [Figure 3]. Mast cell cytoplasm was also similarly stained. Stromal cells and endothelium were negative for MMP-9. MMP-2 was found to be negative in all cellular components throughout the lesion.

The stroma of glomus tumors is generally fibrous. Prominent
stromal myxoid degeneration is an uncommon finding.\[3-5\] Mentzel et al,\[3\] reported 6 cases of glomus tumors showing myxoid stromal changes and associated co-expression of actin and CD34 by the tumor cells. The authors also noted that CD34 expression by tumor cells was limited to glomus tumors with myxoid stroma. Interestingly, in the present case, co-expression of actin and CD34 was also associated with MMP-9 expression by the tumor cells. MMPs are a family of proteolytic enzymes involved in the degradation of many constituents of basement membrane and extracellular matrix, and they are known to play a role in the tumor invasion and metastasis. MMP-9 is also known as 92 kD gelatinase (gelatinase-B).\[6\] Hence it may be speculated that the myxoid stromal change in the present case may be related to MMP-9 expression by the glomus tumor cells. Hisa et al,\[4\] have reported a correlation between the number of glomus cells and the extent of mucinous degeneration.

However, mast cells are also known to produce MMP-9 to mediate extracellular matrix degradation.\[7\] Regarding this mast cell function, it is also reasonable to assume that MMP-9 released by mast cells might be responsible for the myxoid stromal change encountered in some glomus tumors. Nevertheless, the presence of variable numbers of mast cells is a usual feature for these tumors. Daugaard et al,\[2\] graded the number of mast cells in 18 glomus tumors and found that 3 had many (more than 20 per HPF) stromal mast cells, whereas 14 had few (less than 10 per HPF). In their study, no myxoid change was reported in glomus tumor cases having a large number of mast cells. Though an increase in the mast cell population was noted in the present case, myxoid degeneration cannot be solely attributed to it since MMP-9 was consistently expressed in glomus tumor cells as well. Regarding these findings, contribution of both cells to myxoid degeneration is likely.

In conclusion, besides the co-expression of actin and CD34, we also noted MMP-9 expression by the tumor cells in a glomus tumor with myxoid stroma. It may be assumed that immunophenotypic change of tumor cells to express MMP-9, as well as an increased number of MMP-9–expressing mast cells, may be responsible for this myxoid stromal change in the present case. Additional studies on MMP expression and mast cell quantification in CD34-positive myxoid glomus tumors may highlight this issue.

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Sir,

Amyloidosis is a generic term that signifies the abnormal extracellular tissue deposition of one of a family of biochemically unrelated proteins that share certain characteristic staining properties, including apple-green birefringence of Congo red–stained preparations viewed under polarizing light.[1,2] As a term, 'amyloid' was used historically to define proteins that shared similar microscopic characteristics and affinity for certain stains. The various diseases characterized by deposition of 'amyloid' proteins are similarly heterogeneous but have in common the deposits of fibrillar proteins characterized as 'amyloid' in the dermis. In nodular localized cutaneous amyloidosis, the amyloid is believed to be derived from local plasma cells; in contrast to lichenoid or macular amyloidosis, which have keratinocyte-derived amyloid.[1,2] Amyloid deposits in macular and lichen amyloidosis bind to anti-keratin antibodies and contain sulfhydryl groups, pointing to altered keratin as a source for these deposits. There is no difference in staining characteristics of cytokeratins between macular amyloidosis and lichen amyloidosis.[3] Some argue that the deposition of amyloid in macular and lichen amyloidosis may be the result of frequent itching and scratching.[4] The concept has arisen of focal epidermal damage and filamentous degeneration of keratinocytes, followed by apoptosis and conversion of filamentous masses (colloid bodies) into amyloid material in the papillary dermis, perhaps with a contribution from the dermal-epidermal junction.[5] It has been proposed that in lichenoid and macular amyloidosis, specific immunologic tolerance to the presence of keratinocyte-derived apoptotic bodies in the papillary dermis favors their transformation into amyloid by macrophages or fibroblasts; whereas in lichen planus, an autoimmune disorder, a brisk inflammatory response ensures their removal.[6]

Transglutaminase 2 (TG2) is a unique member of an enzyme family (EC 2.3.3.13) because in addition to its primary enzymatic activity of Ca\(^{2+}\)-dependent transamidation of polypeptide chains through their glutamine and lysine residues (or through polyamines), it also binds GTP (which blocks transamidation) and may act as a G protein. It is often up-regulated in cells undergoing apoptosis. In addition, another important role is attributed to TG2: the prevention of tissue injury, inflammation, and autoimmunity once the apoptosis has already been initiated. This function of TG2 is partially achieved by being expressed and activated also in macrophages digesting apoptotic cells and mediating a crosstalk between dying and phagocytic cells. Generally from the in vivo results obtained in some laboratories, it has been proposed that the most important role of TG2 in vivo is to ensure that apoptosis is finished without causing inflammation necrosis and apparent tissue injury. Besides facilitating apoptosis, induction of TG2, and enhancing phagocytosis, TGF\(\beta\) was shown to be required for the proper down-regulation of pro-inflammatory cytokine production in macrophages as well. If, however, necrosis still occurs, TG2 promotes both tissue stability and repair. In TG2−/− animals, all these anti-inflammatory actions are compromised, which results in the appearance of inflammatory cells at the apoptotic sites in the short term and autoimmunity in the long term.[7,8]

Moreover, it merits noting that transglutaminase is suggested to play a role in the pathogenesis of Dutch-type hereditary amyloidosis and Alzheimer’s disease by cross-linking proteins into insoluble polymers.[9]

Letters to Editor

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