

MAST CELLS IN SOLITARY GLOMUS TUMORS: A POSSIBLE ALLOGENIC ROLE

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Abstract. Mast cells in three cases of solitary glomus tumor were examined by light and electron microscopy. As seen by light microscopy, a number of round, oval or elongated mast cells were distributed throughout the stromal connective tissue and showed slight or moderate metachromasia when stained with toluidine blue (pH 4.1). Electron microscopy revealed various types and degrees of degranulation of mast cell granules, and also disclosed a close correlation between mast cells and non-myelinated nerve fibers. These findings suggest that mast cells may play an allogenic role in solitary glomus tumors, probably mediated by the contents, mainly histamine, concentrated in their granules.

Key words: Mast cells; Solitary glomus tumors; Degranulation; Electron microscopy; Histamine; Pain

Solitary glomus tumor is one of a variety of painful skin tumors. It usually causes severe paroxysmal pain or tenderness with some duration. Various factors, such as adjacent Paccinian corpuscles (13), dilatation of tumor vessels (3), concentration of tumor cells (17), mast cells (14), and plentiful distribution of afferent nerves (15), have been hypothetically blamed for causing the pain. However, the mechanism whereby pain arises has not yet been demonstrated in solitary glomus tumors. In the present study, we have obtained two new findings which we suggest may explain the mechanisms.

MATERIALS AND METHODS

Three cases of solitary glomus tumor (Table I) were examined by light and electron microscopy.

Light microscopic studies. 10% formalin-fixed and paraffin-embedded sections were stained with hematoxylin and eosin, periodic acid-Schiff (PAS) with and without diastase digestion, and toluidine blue (pH 4.1 and 2.5).

Electron microscopic studies. One-half of each specimen was fixed for 2 hr in 2% glutaraldehyde in Millonig's phosphate buffer at pH 7.3, and rinsed overnight in the same buffer. The specimens were then post-fixed for 2 hr in 1% osmium tetroxide in the same buffer. They were dehydrated in graded ethanols, substituted by QY-1, and embedded in epoxy resin. After polymerization of the resin for 72 hr at 53°C, the blocks were cut into ultrathin sections and stained with uranyl acetate and lead citrate. Photomicrographs were taken on a Hitachi HU-12AS electron microscope at 80 kV.

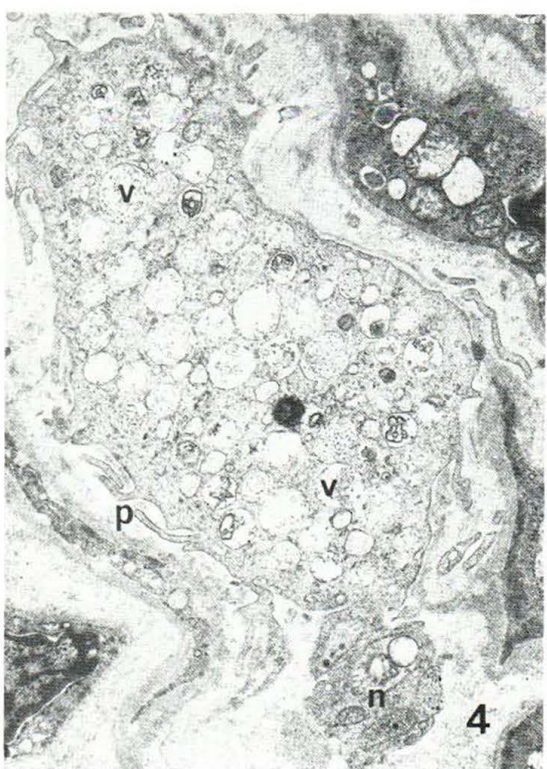
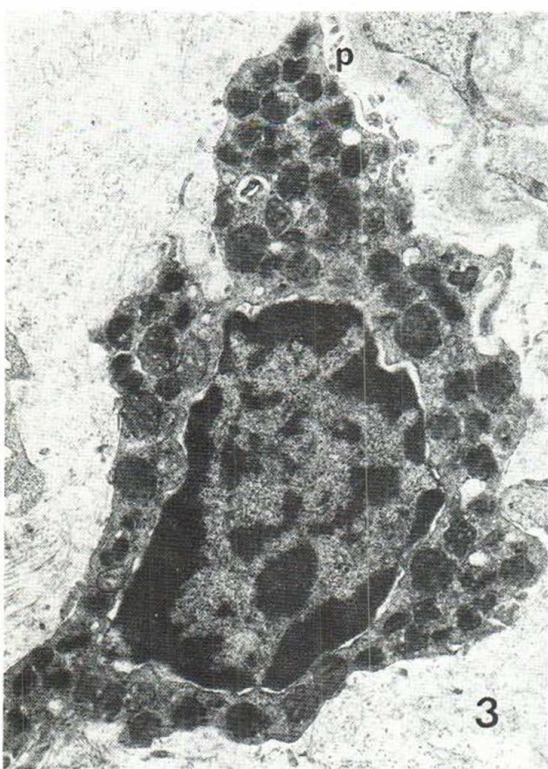
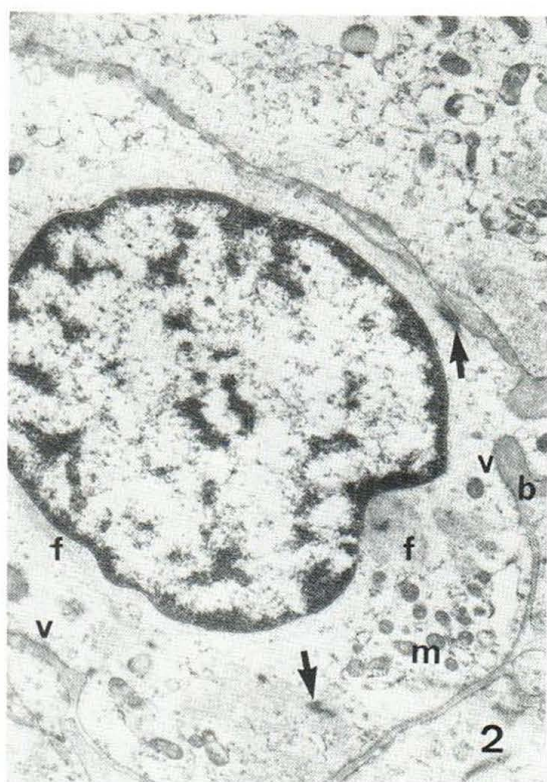
RESULTS

Light microscopy. Each tumor was a typical glomus tumor consisting of clusters of round, oval, or elongated tumor cells which surrounded vascular channels covered by a layer of endothelial cells (Fig. 1). Numerous mast cells were observed in the mucopolysaccharide-rich stroma between clusters of tumor cells (Fig. 1). Mast cells showed not only diastase-resistant, PAS-positive staining, but also slight or moderate metachromasia with toluidine blue stain at pH 4.1.

Electron microscopy. Tumor cells showed ultrastructural similarities to smooth muscle cells. These cells contained varying numbers of fine filaments, 50 to 70 Å in diameter, with focal condensations. Many pinocytotic vesicles and a monolayer of basal lamina were also observed (Fig. 2).

Table I. *Present cases of solitary glomus tumor*

Case	Age	Sex	Site	Onset	Size (mm)	Subjective symptoms
1	52	F	Thumb (subungual)	10 Years	12×7	Tenderness, pain
2	34	F	Little finger	7 Years	2×2	Tenderness
3	22	F	Little finger	1 Month	2×2	Tenderness



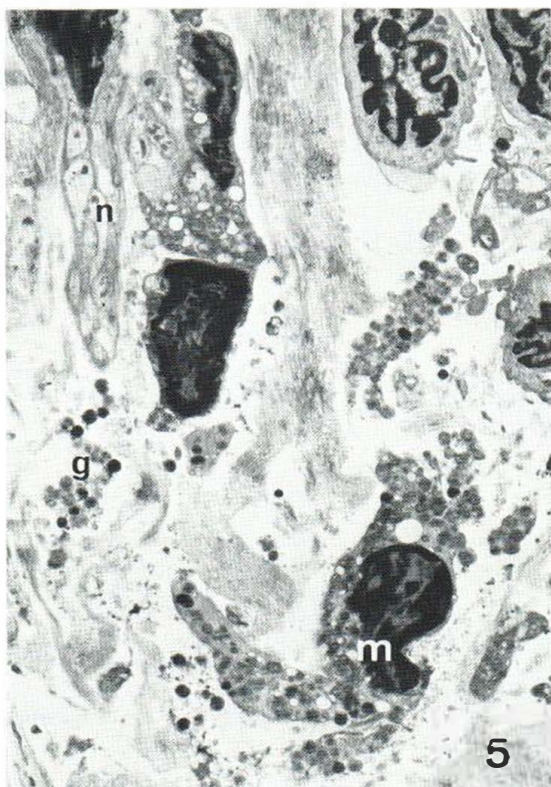


Fig. 5. A mast cell (*m*) showing the 2nd type of degranulation. Degranulated granules (*g*) are seen adjacent to a non-myelinated nerve (*n*). $\times 3\,750$.

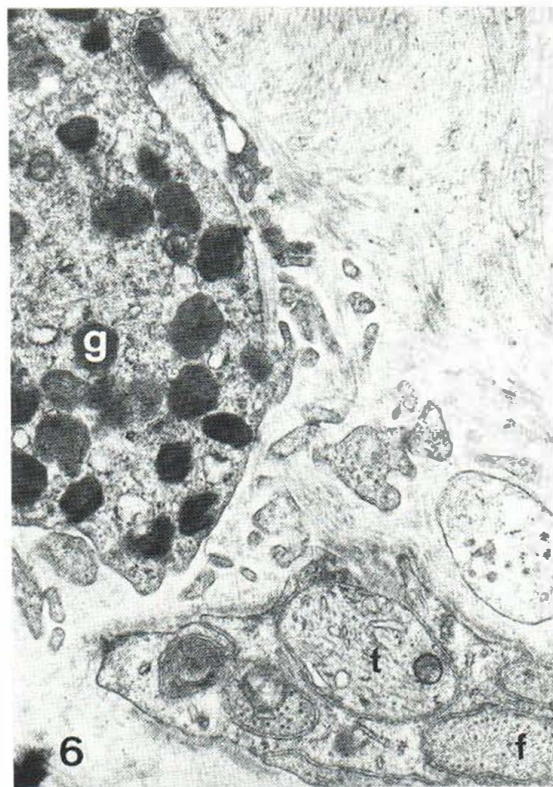


Fig. 6. Close correlation between a mast cell and a non-

myelinated nerve, showing cross and longitudinal sections of neurotubules (*r*) and neurofilaments (*f*). *g*: Mast cell granules. $\times 17\,500$.

Mast cells, round, oval, polyhedral or elongated in shape, showed various numbers of finger-like projections of plasma membrane and were filled with characteristic granules having finger-print-like lamellar structures and a limiting membrane (Fig. 3). A few mast cells contained these granules only in the periphery of the cytoplasm, and other or-

ganelles, such as mitochondria and fine filaments, were distributed in the perinuclear area.

Two new findings were obtained in relation to mast cells. One was the degranulation of mast cell granules. Various types and degrees of degranulation were not infrequently observed. Although mast cells showed all three types of degranulation described by Orfanos (16), the 3rd type, degranulation by formation of vacuoles, was the most frequently observed (Figs. 4, 5). The other was the close correlation between mast cells and non-myelinated nerve fibers. Mast cells not infrequently showed close apposition to or contact with non-myelinated nerves (Figs. 4, 6). Degranulated granules, in parts, were also found near the fibers (Fig. 5).

DISCUSSION

Large or small numbers of mast cells have been observed in various skin tumors (4, 12). When com-

Fig. 1. Clusters of tumor cells surround vascular channels, covered by a layer of endothelial cells. Numbers of mast cells (*m*) lie in the stroma. H & E, $\times 200$.

Fig. 2. Typical tumor cells containing fine filaments (*f*), dense bodies (arrows) and mitochondria (*m*) in the clear cytoplasm. *b*: Basal lamina, *v*: Pinocytotic vesicles. $\times 9\,000$.

Fig. 3. A typical mast cell showing numbers of granules dispersed throughout the cytoplasm. *p*: Villous projections. $\times 15\,000$.

Fig. 4. A mast cell showing both the 3rd type of degranulation and contact with a non-myelinated nerve (*n*). *v*: Vacuolization. *p*: Villous projections. $\times 12\,000$.

pared with normal skin, greater numbers of mast cells are found in pigmented nevus, basal cell carcinoma and neurofibromatosis; fewer in neuroilemmoma, epidermoid carcinoma and malignant melanoma. It has been suggested that mast cells and their products may play a part in the local tissue resistance against the development and growth of tissues and tumors (1, 5).

In glomus tumors, whether solitary or multiple, large numbers of mast cells have usually been observed (8, 14, 19) with only few exceptions (9). In 1968, Murad et al. (14) pointed out the possibility that mast cells might be involved in the production of pain through contraction of tumor cells. However, nothing has been described about the mechanism(s) or the mediator(s).

In the present study, two new findings have been obtained as described above; that is, the degranulation of mast cell granules, and the close correlation between mast cells and non-myelinated nerves. That some of the components of mast cell granules may participate in the process of producing pain is suggested by these findings, for the following reasons: 1) human mast cells contain mainly histamine and heparin in their granules (2, 6), 2) immediate release of highly concentrated histamine from the granules is triggered when the granules are exposed to the extracellular fluid (20), 3) histamine is known to cause either dilatation of arterioles and an increase in capillary porosity or a contraction of most types of smooth muscle, 4) histamine produces pain at high concentrations ($>10^{-5}$ g/ml) (11), 5) histamine may become a neurotransmitter in the central nervous system, 6) release of histamine is provoked by either physical stimuli such as firm pressure and application of heat and cold, or chemical ones (16), and 7) release of histamine from rat mast cells is provoked by acetylcholine in vitro (7); acetylcholine is the most representative neurotransmitter both in neuromuscular junctions of smooth muscle and in neuronal synapses.

Although there is no direct evidence, it is again suggested, from the above findings and reasons, that pain in solitary glomus tumor may be, at least in part, caused by histamine. This concept may be supported by the fact that the solitary glomus tumor usually occurs in the acral region such as fingertips, also usually has rich innervations of non-myelinated and myelinated nerves, and that localized edema in the tumor caused by histamine which is released from mast cell granules may increase tissue pres-

sure, particularly in the acral region, and induce thereby pain. In cutaneous mastocytosis, although degranulation of mast cell granules and close correlation between mast cells and nerves have been also observed (10, 18), there is no pain, probably because of the differences between the localization and architectural forms of the lesions of cutaneous mastocytosis and those of solitary glomus tumors.

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