Multiple Glomus Tumors of the Ankle with Prominent Intranuclear Pseudoinclusions

Glomus tumors are mesenchymal neoplasms that are composed of modified smooth muscle cells of the normal glomus body. Glomus tumors were first described by Wood in 1812 as a painful subcutaneous tubercle, and Mason later described the histological findings in 1924. The normal glomus body is an arteriovenous anastomosing apparatus involved in thermal regulation, which is located in the stratum reticulare of the dermis, primarily in the subungual region, the lateral aspect of the digits and the palm. Histologically, glomus tumor cells are typically small, round with a round nucleus and amphophilic to light eosinophilic cytoplasm.

Glomus tumors are neoplasms that are composed of modified smooth muscle cells of the glomus body. Here, we report a case of multiple glomus tumors of the ankle that showed various histologic types, including the solid type (glomus tumor proper) and angiomatous type (glomangioma). The tumor cells observed in this case also showed prominent intranuclear inclusions, which has not yet been reported in glomus tumors. Ultrastructural examination demonstrated that the nuclear inclusions were not true inclusion bodies but were intranuclear cytoplasmic pseudoinclusions formed by cytoplasmic invaginations that formed as a result of the deep and complex nuclear contours.

CASE REPORT

A 66-year-old woman presented with a painful mass in her left ankle, which had been injured thirty years ago. The patient had been experiencing pain in her left ankle for seven years intermittently and had also been taking oral medication to treat diabetes mellitus for ten years. There were no abnormal findings when the serum chemistry and blood cell counts were analyzed; however an ultrasound revealed two masses, a 3 × 1.3 cm mass posterior to the talus and another 1.6 × 0.7 cm mass near the medial malleolus, which showed heterogeneous and partly cystic appearance. A gun biopsy revealed the presence of only blood clots, however magnetic resonance imaging (MRI)
Fig. 1. Radiologic findings. Plain X-ray of lateral view ankle reveals a soft tissue density mass in the posterior aspect (A). Ultrasound revealed a 3 × 1.3 cm-sized heterogeneous mass at the posterior area to the talus (B). Magnetic resonance imaging (MRI) of the ankle revealed multiple masses at the posterior ankle, suggestive of vascular origin masses (C).

Fig. 2. Gross and microscopic findings of the largest mass (angiomatous type). The mass is ill-demarcated and the cut surface reveals multiple dark brownish spaces, filled with blood clots and yellow soft flesh solid areas (A). The tumor is partly solid and shows many small and large vascular spaces containing thrombi (B). The solid portion around the vascular spaces is composed of small round to polygonal cells with distinct cytoplasmic border (C). The centrally located round to oval nuclei have characteristic intranuclear inclusions (C, inset). The tumor cells are diffusely immunoreactive for smooth muscle actin at the cytoplasm (D).
of the ankle revealed multiple masses at the posterior ankle, which suggested the presence of masses of vascular origin (Fig. 1C). No definite evidence of skeletal metastasis was noted on the whole body bone scan, therefore an excision of the left ankle masses was performed.

**Histological findings**

Although the ultrasound showed only two masses, there were actually three masses present in the ankle. The two tumors were $2.4 \times 1.7$ cm and $1.2 \times 0.8$ cm, and the third mass, measured from the lateral aspect of ankle, was $0.8 \times 0.5$ cm. The cut surface revealed multiple dark brownish spaces that were filled with blood clots and yellow soft flesh solid areas (Fig. 2A). The masses were ill-demarcated with the adjacent fat tissue.

Microscopically, the largest mass was encapsulated by a thick collagenous capsule, however, the capsule had been partially invaded by the tumor. In addition, there were many small and large vascular spaces scattered throughout the mass, with the largest vascular space ($1.5 \times 0.8$ cm) containing thrombi that showed many cholesterol clefts. The solid portion around the vascular spaces was composed of small round to polygonal cells that had a distinct cytoplasmic border, which is consistent with angiomatous type glomus tumors (Fig. 2). The round to oval nuclei were centrally located, and had inconspicuous nucleoli and moderate chromatin clumping. Characteristically, most of the nuclei had intranuclear inclusions, and no mitotic figures were noted. The immunohistochemical analysis revealed that the $\alpha$-smooth muscle actin was diffusely expressed in the cytoplasm of the tumor cells (Fig. 2D).

The other two small masses were more solid, with only a few capillary-sized vascular spaces and no tumor capsule. The cyto-logic features of the smaller masses were the same as those of the largest mass, and were consistent with solid type glomus tumors, including the intranuclear inclusions (Fig. 3).

**Ultrastructural findings**

The tumor was composed of sheets of polygonal cells that were separated by collagen fibers. The nuclei were ovoid-shaped and had very irregular contours due to deep and complex cytoplasmic invaginations. In addition, the tumor showed intranuclear pseudoinclusions that were actually invaginated cytoplasm and the cytoplasm contained a few swollen mitochondria and actin-like filaments (Fig. 4).

**DISCUSSION**

Glomus tumors account for only 1 to 4.5% of all tumors of the hand and seventy five percent of glomus tumors occur in the upper and lower extremities, especially in the subungual areas of hand. Other common sites in which glomus tumors occur include the palm, wrist, forearm and foot, with 19% of glomus tumors occurring in the lower extremities. However, only a few cases of glomus tumors in the ankle have been reported.

Glomus tumors have been divided into the following three types based on the relative proportions of glomus cells, vascular structures and smooth muscle tissue in the mass: glomus tumor proper, glomangioma and glomangiomyoma, however, Masson originally described the 3 distinctive types of tumors as mucoid-

![Fig. 3. Microscopic findings of the small masses (solid type). The small solid tumors show distinct but irregular margin (A). A few small vascular spaces continuous to the tumor cells are noted. The round glomus cells show prominent intranuclear inclusions (B).](image-url)
hyaline type (type I), solid type (type II) and angiomatous type (type III) based on their cellular appearances. The largest mass observed in the case described in this paper can be categorized as glomangioma (type III; angiomatous type) and the two smaller masses described here can be characterized as glomus tumor proper (type II; solid type). The presence of multiple glomus tumors comprising two different histologic types is extremely rare and only two cases have been described to date in the English literature. Both of the previously described cases involved a combination of the solid type and angiomatous type of glomus tumors, similar to the case described herein.

The histology of our case is unique due to the intranuclear inclusions that were present throughout the tumors. Electron microscopic examination of the tumor described here confirmed the nature of the inclusions to be pseudo-inclusions caused by invagination of the cytoplasm deeply into the nucleus with complexity. There has been only one case report of a glomus tumor with intranuclear cytoplasmic inclusions described to date, and this case involved a glomus tumor of the stomach with inclusions that occurred very occasionally.

Intranuclear cytoplasmic pseudo-inclusions are observed in fine-needle aspiration and tissue biopsy specimens obtained from patients with various thyroid diseases including papillary carcinoma, Hashimoto's thyroiditis, follicular adenoma, medullary carcinoma, follicular carcinoma, as well as in cases of balloon cell melanoma, melanocytic nevi, pituitary adenoma, paraganglioma, pheochromocytoma, and adrenal cytomegaly. However, the nature of intranuclear inclusions differs depending on the underlying mechanisms. In cases of meningioma, intranuclear inclusions are divided into intranuclear cytoplasmic pseudo-inclusions and nuclear vacuoles. True intranuclear inclusion bodies of melanocytic nevi that occurred as a result of viral infec-

Fig. 4. Ultrastructural findings. The tumor is composed of sheets of polygonal epithelioid cells separated by collagen fibers (A). The nuclei are ovoid-shaped and have very irregular contours due to deep and complex cytoplasmic invaginations (B, asterix). The nuclei show intranuclear pseudo-inclusion which is actually invaginated cytoplasm (C, thick arrow). The cytoplasm contains a few swollen mitochondria and actin-like filaments (D).
tion have been described by Hahm GK et al.\textsuperscript{13} whereas biotin-rich intranuclear inclusions have been observed in the cribiform monular variant of papillary carcinoma of the thyroid, uterine and ovarian endometrioid adenocarcinoma, colonic adenoma and adenocarcinoma, pancreaticoblastoma, pyloric gland-type adeoma and morule-lacking adenocarcinoma of the gallbladder.\textsuperscript{16}

In cases of pulmonary adenocarcinoma, a large majority of the intranuclear inclusions are pseudoinclusions that occur due to invagination of the nuclear envelope, which is similar to what was observed in this case.\textsuperscript{17} However, the true intranuclear inclusions described by Hiroshima et al.\textsuperscript{18} in a case of pulmonary adenocarcinoma were classified into two types when samples were analyzed using light microscopy and into three types when electron microscopy was used. The inclusions were classified into eosinophilic inclusion bodies with a clear halo around the inclusions and faintly eosinophilic inclusion bodies surrounded by condensed chromatin without a halo when light microscopy was used to analyze the samples. However, when electron microscopy was used, the samples were classified into type A which showed aggregation of electron dense particles and an electron-dense core, type B, which consisted of a mass of branching and whirlng tubular structures and type C, which was comprised of two or more spherical inclusion bodies.\textsuperscript{19} The intranuclear inclusions observed in our case are different from these true inclusions because they do not contain specific organelles or electron dense particles but are instead formed by the cytoplasm as a result of irregular nuclear invagination. Although intranuclear inclusions have been observed in pigmented villonodular synovitis\textsuperscript{19} and hepatocellular carcinoma\textsuperscript{20}, the nature of the invaginations in these cases have not been investigated.

The ultrastructural findings of glomus tumors are very similar to those of smooth muscle neoplasm with actin-like filaments, dense bodies, pinocytosis and basal lamina being common to both of these types of tumors.\textsuperscript{1} However, glomus tumors are composed of rounded or polygonal cells that have a rounded nucleus and occasional clefs and prominent nucleoli. In addition, the cytoplasm of cells in glomus tumors are filled with condensed chromatin and endoplasmic reticulum.\textsuperscript{4} Although we observed some actin-like filaments that corresponded to the smooth muscle actin immunoreactivity, the dense bodies and pinocytosis could not be definitely identified in the tumor cells because they had been fixed in formalin. The nuclear contour clearly demonstrated that the intranuclear inclusions were caused by cytoplasmic pseudoinclusions created by the invaginated cytoplasm due to the deep and complex nuclear contours. Overall this case which involved glomus tumors that contained prominent intranuclear cytoplasmic pseudoinclusions throughout the tumor shows that glomus tumors can readily demonstrate prominent intranuclear inclusions.

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