

CASE REPORT

MALIGNANT GLOMUS TUMOR OF THE FOOT WITH OBVIOUS NEUROENDOCRINE DIFFERENTIATION: A CASE REPORT WITH IMMUNOHISTOCHEMICAL STUDIES

TADASHI TERADA

Department of Pathology, Shizuoka City Shimizu Hospital, Shizuoka, Japan

Obvious neuroendocrine differentiation has not been reported in glomus tumor. The author herein reports a malignant glomus tumor of the foot showing obvious neuroendocrine differentiation. A 63-year-old woman presented with tumor of the left foot. The tumor was superficially seated, and located in the dermis. It was completely resected with wide margins. It measured $0.7 \times 0.7 \times 0.6$ cm. Microscopically, the tumor was composed of atypical epithelioid cells located around blood vessel-like structures. The epithelioid cells showed relatively clear cytoplasm and severe cellular atypia, and resembled basal cell carcinoma. Focal areas of squamoid differentiation, carcinoid patterns, and neural differentiations were seen. There was no necrosis or atypical mitosis. However, mitotic figures were seen in 16 per 50 high-power-fields (HPF). The hematoxylin and eosin (HE) diagnosis was basosquamous carcinoma. Immunohistochemically, the tumor cells were strongly positive for vimentin, α -smooth muscle actin, and neuron-specific enolase. The tumor was focally positive for NCAM, synaptophysin and chromogranin. The blood vessel-like structures had a layer of CD31- and CD34-positive endothelial cells. Tp53 was positive and the Ki-67 labeling index was 23%. The tumor cells were negative for cytokeratin (CK) AE1/3, CK CAM5.2, CK5, CK6, CK7, CK8, CK14, CK18, CK19, CK20, p63, EMA, CEA, CA19-9, desmin, myoglobin, HMB-45, Melan-A, S100 protein, MUC1, MUC2, MUC5AC, and MUC6. Taken together with HE histology, the tumor was labeled as malignant glomus tumor with neuronal differentiation, based on the classification system of Folpe *et al.* The post-pathological diagnosis whole body examination using CT, MRI, PET, and endoscopies identified no tumors. The patient is now free from tumor and healthy 18 months after the resection.

Key words: glomus tumor, malignant, neuroendocrine, immunohistochemistry.

Introduction

The recent recognition of the concepts of perivascular myoid cell phenotype and perivascular epithelioid cell phenotype has changed the concept of angiogenic tumors, in particular “hemangiopericytoma”-like tumors [1, 2]. The perivascular myoid cell concept has yielded the recognition of myoperi-

cytoma [3-8], myofibroma [4], myofibromatosis [9], angioleiomyoma [10], and glomus tumors (GTs) [9, 11, 12], while the perivascular epithelioid cell concept that shows melanocytic lineage has led to the recognition of PEComa [13, 14], clear cell sugar tumor [15, 16], angiomyolipoma [17], and lymphangiomyomatosis [1]. These tumors belong to a spectrum of perivascular myoid cell tumors and perivascular

epithelioid cell tumors, and there are some overlaps among these entities.

Glomus tumor is a rare tumor that recapitulates the appearances of the perivascular myoid cells of the normal glomus body. Malignant GT (MGT) is very rare, and only a few cases have been reported [18-25]. The malignancy of GT is now based on the system proposed by Folpe *et al.* in 2001 [12]. Obvious neuroendocrine features of GT have not been reported. The author herein reports on a case of MGT of the foot showing obvious neuroendocrine differentiation.

Case report

A 63-year-old woman consulted our hospital because of a small tumor of the left foot. The tumor was superficially situated, and located in the dermis. The tumor was completely resected with wide margins. The tumor measured $0.7 \times 0.7 \times 0.6$ cm.

Microscopically, the tumor was located in the dermis, and well defined from the surroundings with focal capsules. No lymphovascular permeation was seen. The surgical margins were negative; thus the tumor was completely resected. The tumor was composed of atypical epithelioid cells located around blood vessel-like structures (Figs. 1A and 1B). The epithelioid cells had relatively clear cytoplasm and had severe cellular atypia and resembled basal cell carcinoma (Figs. 1B and 1C). Focal areas of squamoid differentiation (Fig. 1D), carcinoid patterns (Fig. 1E), and neuroid differentiation (Fig. 1F) were seen. There were close associations between tumor cells and nervous tissues. There was no necrosis or atypical mitosis. However, mitotic figures were seen in 16 per 50 high power fields (HPF). The hematoxylin and eosin (HE) diagnosis was basosquamous carcinoma.

An immunohistochemical study was done using Dako-Envision methods, as previously reported [26-31]. Immunohistochemically, the tumor cells were strongly positive for vimentin (Fig. 2A), α -smooth muscle actin (ASMA) (Fig. 2B), and neuron-specific enolase (NSE) (Fig. 2C). The tumor was focally positive for NCAM (Fig. 2D), synaptophysin (Fig. 2E) and chromogranin (Fig. 2F). The blood vessel-like structures had a layer of CD31- and CD34-positive endothelial cells (Fig. 2G). The p53 was positive (Fig. 2H) and the Ki-67 labeling index was 23%.

The tumor cells were negative for cytokeratin (CK) AE1/3, CK CAM5.2, CK5, CK6, CK7, CK8, CK14, CK18, CK19, CK20, p63, EMA, CEA, CA19-9, desmin, myoglobin, HMB-45, Melan-A, S100 protein, MUC1, MUC2, MUC5AC, and MUC6. Taken together with HE histology, the tumor was labeled as malignant GT with neuronal differentiation, based on the classification system of Folpe *et al.* [12].

The post-pathological diagnosis whole body examination using computed tomography (CT), magnetic

resonance imaging (MRI), positron emission tomography (PET) and endoscopies identified no tumors. The patient is now free from tumor and is healthy 18 months after the resection.

Discussion

The present tumor was superficially seated in the foot. The tumor was composed of epithelioid polygonal cells with severe cellular atypia. The tumor cells were located around the vascular structures. Immunohistochemically, the tumor cells were positive for vimentin and ASMA, and negative for S100 protein, Melan-A and HMB-45. These histological features are those of glomus tumor (GT) [9, 11, 12].

According to Folpe *et al.* [12], the GTs are classified into the following 4 categories: MGT, symplastic GT, GT of uncertain malignant potential, and glomangiomas. Malignant GT is characterized by tumors with a deep location and a size of more than 2 cm, or atypical mitotic figures, or moderate to high nuclear grade and 5 or more mitotic figures per 50 HPF. Symplastic GT is characterized by tumors with high nuclear grade in the absence of any other malignant features. Glomus tumor of uncertain malignant potential is characterized by tumors that lack criteria of malignant GT or symplastic GT but have high mitotic activity and superficial location only, or large size only. Glomangiomas is characterized by tumors with histological features of diffuse angiomas and excess of glomus cells.

The present tumor is apparently MGT based on Folpe's criteria [12]. It showed marked nuclear atypia and many mitotic figures (16 per 50 HPF). It did not have necrosis, deep location, or a large size > 2 cm. The p53 was strongly positive, suggesting mutations of the p53 gene and malignant nature of tumor. The Ki-67 labeling was very high (25%), indicating high cell proliferation and suggesting the malignant potential of the tumor.

Although the present tumor fulfills the criteria of MGT according to Folpe [12], there seem to be opinions that the cellular atypia is not sufficient to diagnose MGT in the present case. The follow-up period (18 months) of the present case is relatively short. However, the author thinks that the present tumor is malignant because it fulfilled Folpe's criteria for MGT [12]. Certainly, the follow-up period (18 months) is relatively short, but it is quite likely that the tumor is completely removed by the surgery, which was proved by the pathological examinations showing completely negative surgical margins. Thus, it is probable that the present tumor is malignant. However, it is believed that individuals having tumors labeled as MGT can show benign characteristics. In any case, the patient needs strict follow-up because it was histologically diagnosed as malignant.

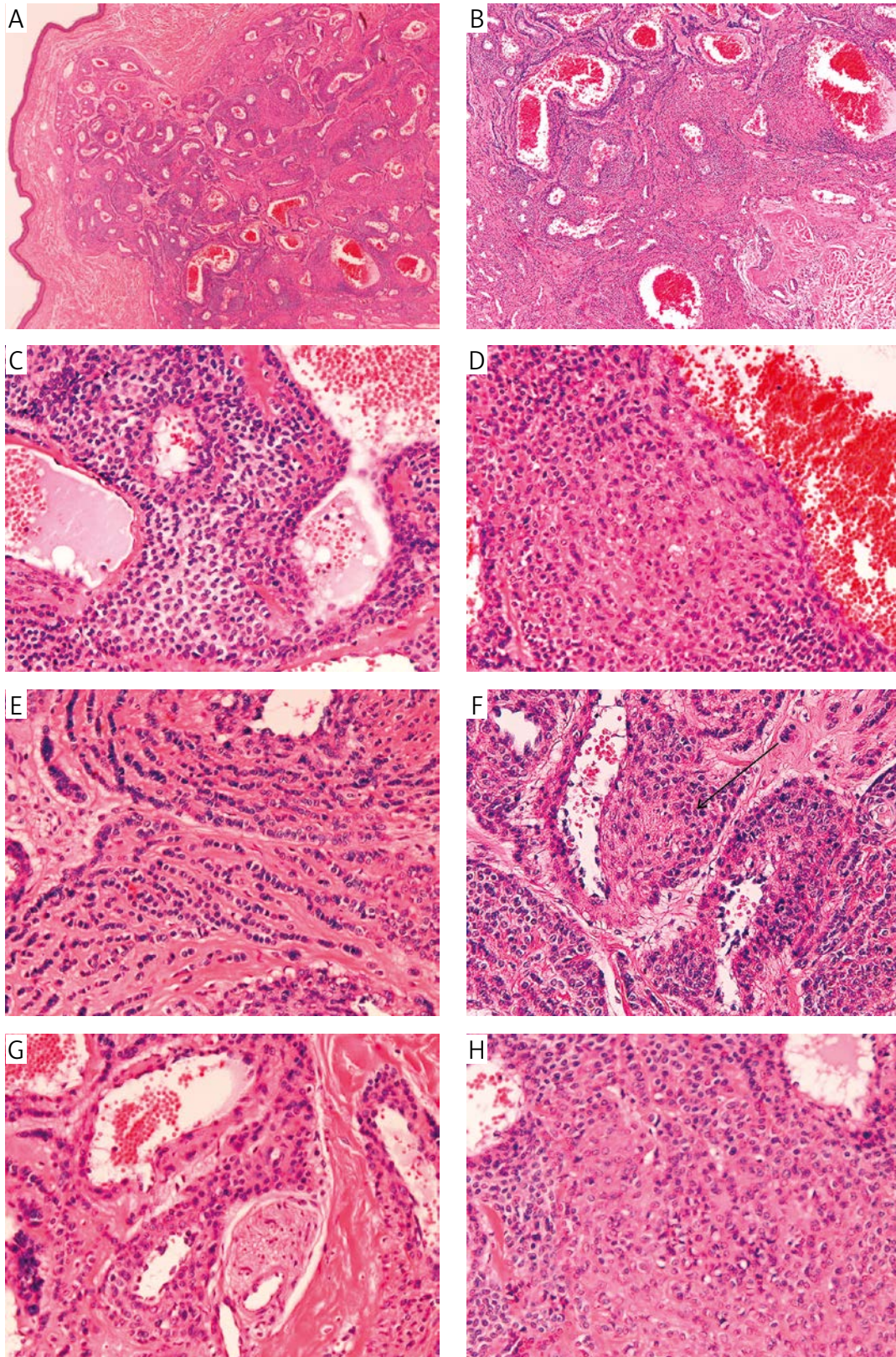


Fig. 1. Histology of the tumor. **A)** Very low power view of the tumor. The tumor is located in the dermis, and is well defined. No infiltrative growth is seen. The tumor shows proliferation of basaloid cells and shows features of basal cell carcinoma except for the angiomatoid structures. HE, magnification 20 \times . **B)** Medium sized magnification. The tumor shows basaloid cells and angiomatoid structures. HE, magnification 40 \times . **C)** High power view. The tumor is composed of basaloid clear cells with angiomatoid features. HE, magnification 200 \times . **D)** Focal areas show squamous cell differentiation. HE, magnification 200 \times . **E)** Focal areas show carcinoid or rippenoid patterns consistent with basal cell carcinoma or neuroendocrine carcinoma. **F)** Very frequently, the tumor cells show neurooid differentiation (arrow). HE, magnification 200 \times . **G)** Very frequently, there were close associations between tumor cells and relatively mature neuronal cells. HE, magnification 200 \times . **H)** The tumor cells shows many mitotic figures. HE, magnification 200 \times

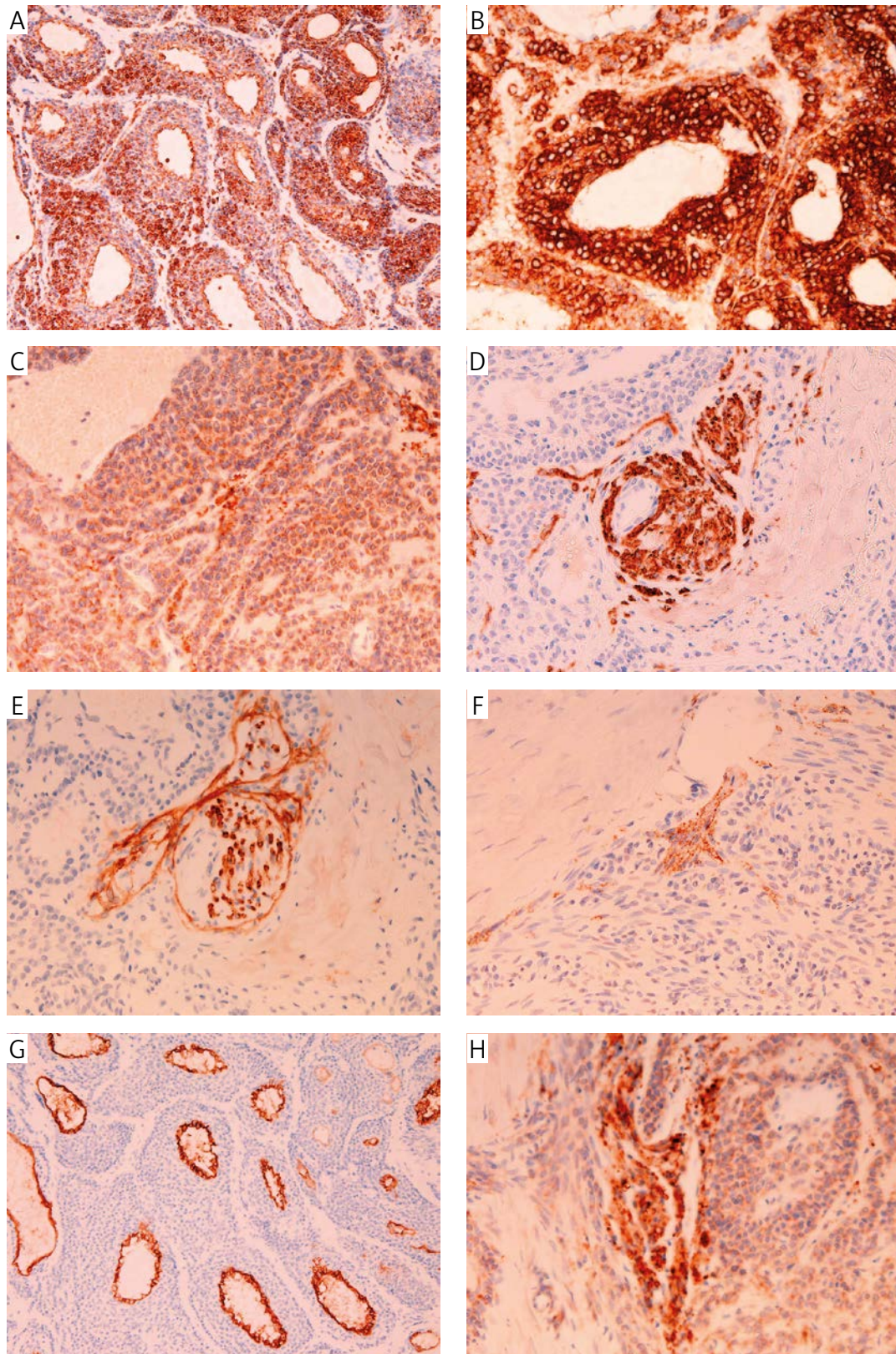


Fig. 2. Immunohistochemical features of the tumor. The tumor cells were strongly positive for α -smooth muscle actin (A) and neuron-specific enolase (B). The tumor was focally positive for NCAM (C), synaptophysin (D) and chromogranin (E). The blood vessel-like structures had a layer of CD31- and CD34-positive endothelial cells (F). A-F: magnification 200 \times . The blood vessels-like structures had a layer of CD31- and CD34-positive endothelial cells (G). The p53 was positive (H) and Ki-67 labeling index was 23%. A-H: magnification 200 \times

It is well known that MGT may show an aggressive clinical course [18, 19]. The GT of the present patient did not show recurrence or metastasis 18 months after the resection. The patient is now being followed up carefully.

In the present study, the HE diagnosis was basosquamous carcinoma (BSC). The tumor first appeared on HE preparation as basal cell carcinoma (BCC). The tumor cells were basaloid, and epithelioid, and had significant atypia including mitotic figures. Squamoid differentiations were frequently seen, and there were carcinoid (ripenoid) patterns compatible with BCC. Such carcinoid and squamoid patterns appear to be extremely rare in MGT. The author's HE diagnosis was BSC, and the author was surprised by the immunohistochemical features indicating that the tumor cells showed no epithelial lineage but showed myopericytomatous characteristics. Thus, on HE preparations, the MGT should be differentiated from BCC and BSC. The author stresses that MGT may show histologies of BCC, carcinoid (ripenoid), squamous cell differentiation, and BSC on HE preparations. The basaloid nature, carcinoid (ripenoid) patterns and apparently squamous differentiation seen in the present MGT should be investigated further.

Differential diagnosis of GT includes other perivascular myoid cell tumors. Myopericytoma usually does not show epithelioid features of tumor cells, and shows nodularities of tumor cells [3-8]. Myopericytoma is positive for α -smooth muscle actin [3-8]. However, the histological features of the present tumor are different from myopericytoma. The present tumor is different histologically from other perivascular myoid cell tumors, including myofibroma [4], myofibromatosis [9], and angioleiomyoma [10]. Myofibroma and myofibroblastoma show much more fibrotic areas, and the tumor cells are not polygonal. Angioleiomyoma (vascular leiomyoma) shows a combination of smooth muscles and vasculatures, and the tumor cells do not show epithelioid morphologies. The present case is not different from angiomatoid malignant fibrous histiocytoma (MFH) because of absence of storiform-pleomorphic and other patterns of angiomatoid MFH.

The present tumor is different from perivascular epithelioid cell tumors, such as PEComa [13, 14]. PEComa usually shows immunoreactivity of HMB45, Melan-A, and S100 protein [13, 14], and is histologically composed of clear cells with large hyperchromatic bizarre nuclei. The present tumor is histologically and immunohistochemically different from other perivascular epithelioid tumors including clear cell sugar tumor [15, 16], angiomyolipoma [17], and lymphangiomyomatosis [1]. Clear cell sugar tumor mainly occurs in the lung and is composed of epithelioid clear cells. Angiomyolipoma shows a combina-

tion of vasculatures, smooth muscles, and fat tissue. Lymphangiomyomatosis most commonly occurs in the lung. It is characterized by lymphatic-like spaces lined by myoid cells. These perivascular epithelioid tumors show immunoreactivity for S100 protein and melanosome proteins (HMB45 and Melan-A).

One of the most important and quite interesting findings in the present MGT is that the MGT has obvious neuroendocrine features. In the HE preparations, neuroid differentiations were frequently seen, and there were close associations between the tumor cells and relatively mature neurons. In addition, immunohistochemically, the tumor cells were diffusely and strongly positive for NSE. The tumor cells were also positive for NCAM, synaptophysin, and chromogranin. These immunohistochemical data support the HE histological observations that showed neuroid differentiation. Taken together with HE histology, it is concluded that the present MGT has neuroid or neuroendocrine features. Although many epithelial carcinomas may show focal neuroendocrine features, such an apparent phenomenon in GT has not been reported. Neuroendocrine differentiation is very rare in mesenchymal tumors.

There are several reports of focal neuroendocrine differentiation in GT, particularly gastric GT. Herein, most comprehensive investigations are mentioned. Wang *et al.* [32] reported that focal synaptophysin positivity was seen in 2/11 gastric GT, but no immunoreactivity for NCAM (0/11), NSE (0/11), or chromogranin (0/11). They also demonstrated ultrastructurally endocrine granules in some gastric GT. Miettinen *et al.* [33] found synaptophysin reactivity in 3/32 gastric GT. Kim *et al.* [34] observed ultrastructurally endocrine-type granules in one GT. Farrior *et al.* [35] noted endocrine activity of glomus jugulare tumors. Lawson *et al.* [36] found endocrine cells in the glomus jugular apparatus in carotid arteries. Of these comprehensive studies, the neuroendocrine features in GT of stomach and other sites are not prominent but only sparse. The ultrastructural endocrine granules also lacked conclusive findings of real endocrine granules. These GTs of stomach and other sites seem not to be authentic endocrine differentiation but only represent focal endocrine differentiation that is frequently seen in other neoplasms. In contrast, the GT of the present case shows obvious neuroendocrine features not considered as only neuroendocrine differentiation. Any way, comprehensive studies of neuroendocrine features in GT are mandatory in future. The author's previous work [37-52] showed that human embryonic and fetal smooth muscle cells and stem cells in the gastrointestinal tract show neuroendocrine antigens (NCAM, NSE, synaptophysin, and chromogranin), which are also markers of stem cells in developmental biology, in addition to KIT, PDGFRA, CD34, ErbB2, MET,

and bcl-2. This finding supports the observation that a tumor with smooth muscle antigens also shows neuroendocrine phenotypes.

The implications of these neuroid or neuroendocrine features of the present MGT were unclear. Embryology shows that the glomus anlagen and neurons develop from the mesoderm. The association between the two is close in embryology. Thus, it is conceivable that GT may show neuroendocrine or neuroid differentiation. The carcinoid (ripenoid) patterns seen on HE preparations are never seen in conventional MGT, suggesting that the carcinoid pattern is a reflection of neuroendocrine differentiation. It is also possible that the present tumor is a kind of stem cell tumor, because NCAM, NSE, synaptophysin and chromogranin are antigens of stem cells of various types [37]. Other stem cell antigens including CD34 and CK14 were negative in the present study, but this negativity does not exclude stem cell cancer. This concept that GT is a stem cell tumor should be examined by the use of many stem cell antigens and molecular techniques.

In the present study, the tumor cells were negative for CK AE1/3, CK CAM5.2, CK5, CK6, CK7, CK8, CK14, CK18, CK19, CK20 and EMA, indicating that the present tumor is not an epithelial tumor. Tp63 was negative, showing that the present tumor is not squamous cell carcinoma, BCC, or myoepithelial carcinoma. CEA and CA19-9 were negative, suggesting that the present tumor is not adenocarcinoma. Desmin was negative. This negativity is difficult to explain, because GT may be positive for desmin. It is thought that some GTs may be negative for these intermediate filaments present in muscle cells. Myoglobin was negative, indicating that the present tumor shows no rhabdomyomatous differentiation. The meanings of HMB-45, Melan-A, and S100 protein are described in the text. MUC1, MUC2, MUC5AC and MUC6 were negative, indicating that GT does not have mucin core proteins (MUCs).

The author declares no conflict of interest.

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Address for correspondence

Tadashi Terada
 Department of Pathology
 Shizuoka City Shimizu Hospital
 Miyakami 1231 Shimizu-Ku
 Shizuoka 424-8636, Japan
 tel. 81-54-336-1111
 fax 81-54-336-1315
 e-mail: piyo0111jp@yahoo.co.jp