

Solitary neurofibroma of the maxillary sinus: Report of a case

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*Short running title:* Solitary neurofibroma of the maxillary sinus

## **Abstract**

Although neurofibroma frequently occurs as a local manifestation of von Recklinghausen's disease, solitary lesions in the oral and maxillofacial region are rare. Here, we describe an extremely rare solitary neurofibroma that arose in the maxillary sinus of a 41-year-old man. Panoramic radiography and a CT scan showed a slightly swollen maxillary sinus mucosa and a well-circumscribed cystic lesion suggesting a radicular cyst associated with a maxillary molar. The lesions were removed by radical sinusotomy under general anesthesia. A histopathological examination revealed that the nodular lesion of the sinus mucosa was not encapsulated and that it was composed of somewhat increased numbers of spindle cells accompanied by delicate hyperplastic fibers. These cells had flexed, wavy and linear spindle nuclei. Immunohistochemistry revealed that these tumor cells were positive for S-100 and neuron-specific enolase (NSE). A few spindle cells that were positive for  $\alpha$ -SMA within the tumor were thought to be fibroblastic cells (myofibroblasts) derived from the endoneurium or surrounding connective tissue. These findings overall were compatible with the characteristics of neurofibroma. The cystic lesion was diagnosed as a radicular cyst. The patient remained free of tumor recurrence at 26 months of follow-up.

**Key words:** S-100 protein, neuron-specific enolase, peripheral nerve sheath, tumor

## **Introduction**

Peripheral nerve sheath tumors comprise benign Schwannomas and neurofibromas, as well as malignant Schwannomas[1]. Neurofibromas arise from Schwann cells and fibroblasts of the connective tissue of the endoneurium[2,3]. Mast cells and endothelial cells may also be intermingled[2,4]. This tumor tends to develop in the dermis and subcutaneous fat of the trunk and limbs. Multiple cutaneous neurofibroma is a manifestation of neurofibromatosis type 1 (NF-1, von Recklinghausen's disease) and oral neurofibroma often arises in patients with NF-1[1,3-5].

Nerve sheath tumors arising in the maxillary sinus usually reach a considerable size before being diagnosed because they are clinically asymptomatic. Advanced neurofibromas and Schwannomas arising in the maxillary sinus cause pain, epistaxis, nasal obstruction, proptosis and swelling of face and/or oral mucosa. However, these symptoms are nonspecific for neurofibroma[3,6]. Robitaille et al. emphasized the importance of early diagnosis and thorough surgical excision, especially for NF-1-associated neurofibroma[6].

Early benign neurofibroma does not cause bone assimilation, but bone resorption is sometimes discovered in more advanced tumors. Therefore, a preoperative CT scan is useful[3,5]. Scanning by MRI is also helpful for diagnosing neurofibromas as they are usually isointense or have a lower intensity than gray structures on T1-weighted images, and are isointense or have a higher signal on T2-weighted images[3,5]. Heterogeneous contrast enhancement is typical of neurofibromas[3,7].

Solitary neurofibromas of the maxillary sinus are extremely rare[3,8-10].

Here, we describe a patient with a solitary neurofibroma that developed close to a radicular cyst in the maxillary sinus.

## Case report

A 41-year-old man was referred to Nagasaki University Hospital for evaluation of a radiolucent lesion in the right upper molar region. His medical history revealed schizophrenia. An oral examination revealed no symptoms in the right upper molar region. The electric pulp test of the right maxillary molars indicated a non-vital result. Panoramic radiography revealed round, radiolucent lesions of the right upper second molar root apex, and a large radio-opaque area in the lower right maxillary sinus (Fig. 1). A CT scan revealed a solitary cystic lesion extruding to the right maxillary sinus, with a slightly swollen adjoining sinus mucosa (Fig. 2A and B). The patient was clinically diagnosed as having a radicular cyst of the right upper second molar and right maxillary sinusitis. Right maxillary second molar extraction, right maxillary first molar root resection, cystectomy and radical sinusotomy proceeded under general anesthesia. In this case, we extracted the right maxillary second molar in the operation, because the patient was tend to reject the additional dental treatment of this tooth due to the his medical history of schizophrenia, and the horizontal bone absorption of the alveolar bone of the tooth.

A histopathological examination of the sinus mucosa of the mesial maxillary sinus floor (Fig.2A and B) revealed a non-encapsulated submucosal nodule comprising a mixture of proliferative spindle cells and hyperplastic delicate fibers. The cells contained flexed or wavy nuclei in addition to linear spindle nuclei and intermingled with mast cells containing basophilic granules (Fig. 3). Immunohistochemically, the nodule cells with flexed or wavy nuclei were positive for S-100 (Fig. 4) and

neuron-specific enolase (NSE) (Fig. 5). Morbidly fibrotic myofibroblasts as well as smooth muscle, mesothelium and myoepithelial cells contain  $\alpha$ -SMA[11]. A few spindle cells in the nodule were immunoreactive to  $\alpha$ -SMA (Fig. 6). These findings indicated that the nodule was a tumor comprising Schwann and fibroblastic cells. Thus the submucosal lesion of the mesial maxillary sinus floor was histopathologically diagnosed as neurofibroma. The periapical lesion of the molar was a cyst wall comprising granulation tissues covered with stratified squamous epithelium. This lesion was diagnosed as a radicular cyst. The lesions were independent of each other.

A second evaluation of the patients' skin did not uncover either café-au-lait spots or neurofibromas associated with NF-1. These findings confirmed the final diagnosis of solitary neurofibroma of the maxillary sinus. The patient was followed up for 26 months without tumor recurrence.

## Discussion

Neurofibromas comprise solitary tumors and multiple tumors associated with NF-1[3,5,10]. A few reports have described solitary neurofibroma in the maxillary sinus[3,8,9,12]. Hillstrom et al. described that nerve sheath tumors including neurofibroma occur at high frequency in the head and neck region, but only 4% occur within the paranasal sinus[9]. In English literatures, the report of solitary neurofibroma arising in maxillary sinus has been only one case except for our present case since 1990[3]. Therefore, solitary neurofibroma arising in maxillary sinus is extremely rare entity.

A histological examination is essential to confirm a diagnosis of neurofibroma[9]. Histopathologically, neurofibromas usually have no capsule and proliferation outside the perineurium might not appear well demarcated and cells can blend with adjacent connective tissue [13]. Neurofibromas comprise interlacing bundles of elongated cells with wavy and dark-stained nuclei, wire-like strands of collagen and myxoid stroma dotted with occasional mast cells and lymphocytes[10,13]. Neurofibromas might be difficult to distinguish from other non-epithelial tumors especially in small biopsy or curettage specimens because the histological appearance tends to be non-specific[5]. A biopsy or a sufficient amount of specimens is required for macroscopic and microscopic examination, and immunohistochemical studies are essential for exact diagnosis. Immunoreactivity for S-100 protein, NSE and vimentin is characteristic of neurofibromas[3,5,7,9,10]. Although Hirano et al., who described a patient with nasal neurofibroma, stated that neoplastic cells were negative for  $\alpha$ -smooth

muscle actin ( $\alpha$ -SMA)[5], the tumor in our patient contained a few  $\alpha$ -SMA-positive cells. Fibroblasts that are  $\alpha$ -SMA-positive (myofibroblasts) appear and produce extracellular matrix in wound healing[11]. We suggest that the  $\alpha$ -SMA-positive cells identified herein were derived from endoneurial or non-neoplastic fibroblasts in surrounding connective tissues that merged into the tumor. In our case, neurofibroma was detected in the submucosal lesion of the mesial maxillary sinus floor histologically, but the lesion could not be detected in the soft tissue mode CT images. The histopathological examination is essential to make a diagnosis of neurofibroma.

Most neurofibromas of the maxillary and ethmoid sinuses arise from the ophthalmic or maxillary branches of the trigeminal nerve [10,14]. Because the neurofibroma in our patient developed in the maxillary sinus mucosa adjacent to the apical region of a molar, the tumor might have originated in middle superior alveolar nerve or in the superior dental plexus.

The standard treatment for benign peripheral nerve tumors is tumor enucleation. However, complete resection is required for neurofibromas because they are usually not encapsulated and might extensively infiltrate[5]. Some tumors diffusely involve adjacent normal tissues such as nerves and blood vessels, which can complicate complete resection[4]. Therefore, even if the tumor resection is complete, a long-term follow-up is necessary.

Approximately 10% of solitary neurofibromas undergo malignant transformation and their frequency is much lower than that of neurofibromas related to NF-1[3,5,7]. Therefore, further careful follow-up is considered necessary.

In conclusion, we reported the extremely rare case of solitary neurofibroma arising in maxillary sinus mucosa. Our patient has remained free of recurrence for 26 months postoperatively.

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### Figure legends

Fig.1. Panoramic radiography revealed the round, radiolucent lesions of the right upper second molar root apex, and the exceeding of the radio-opaque of the lower area of right maxillary sinus (arrows).

Fig.2A and B. The CT scan showed a solitary cystic lesion extruding to right maxillary sinus (arrows), and adjoin sinus mucosa were slightly swelling (arrow heads).

Fig. 3. Spindle cells proliferate accompanied by hyperplasia of dedicate fibers. Nuclei are linear to wavy. Arrows indicate mast cells (H&E  $\times$  20).

Fig. 4. Immunohistochemical staining for S-100. Cytoplasm of spindle cells is positive ( $\times$  40).

Fig. 5. Immunohistochemical staining for NSE. Most tumor cells are immunoreactive ( $\times$  40).

Fig. 6

Immunohistochemical staining for  $\alpha$ -SMA. Some cells in the tumor are positive ( $\times$  40).

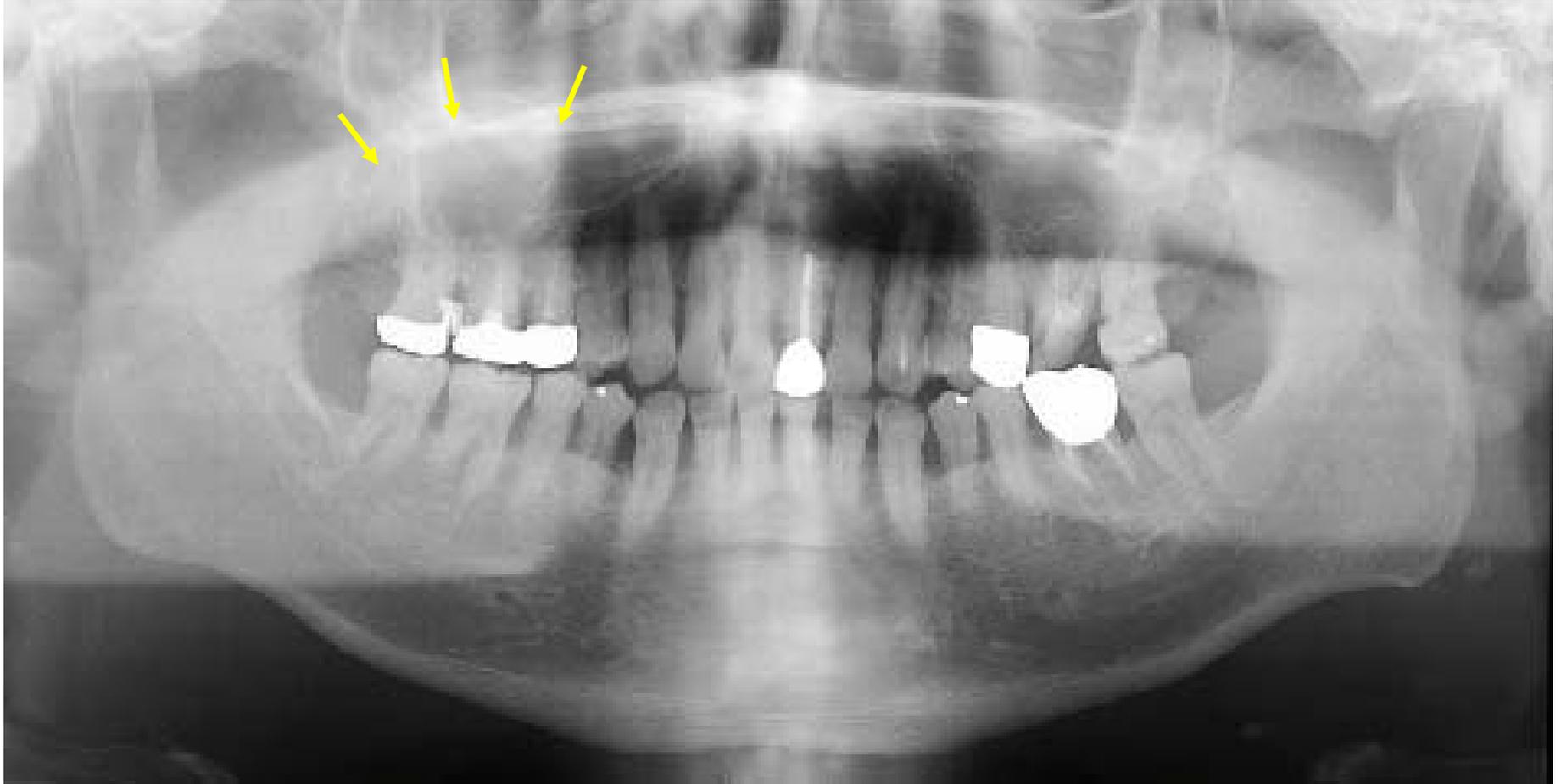


Fig. 1

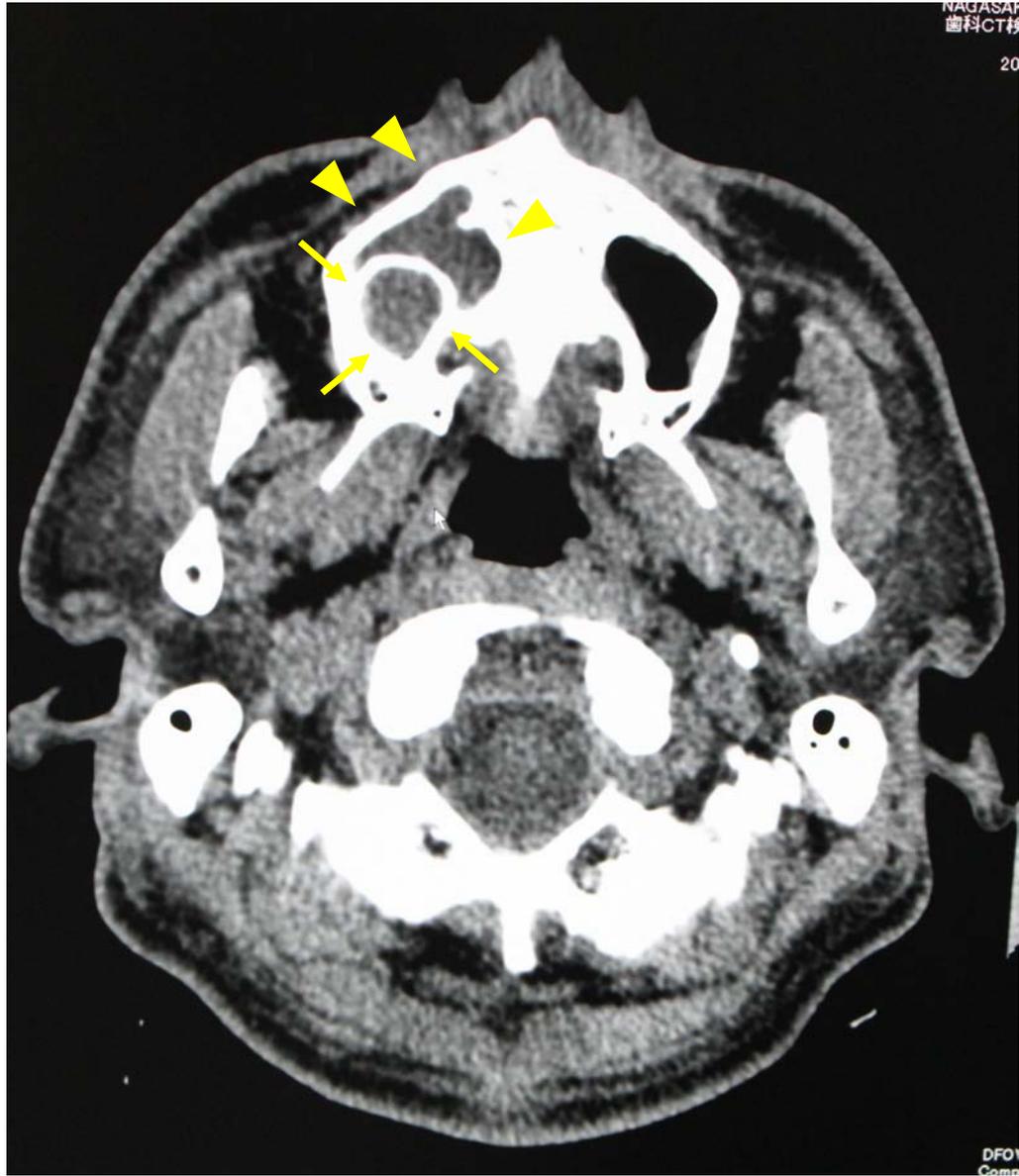


Fig. 2A

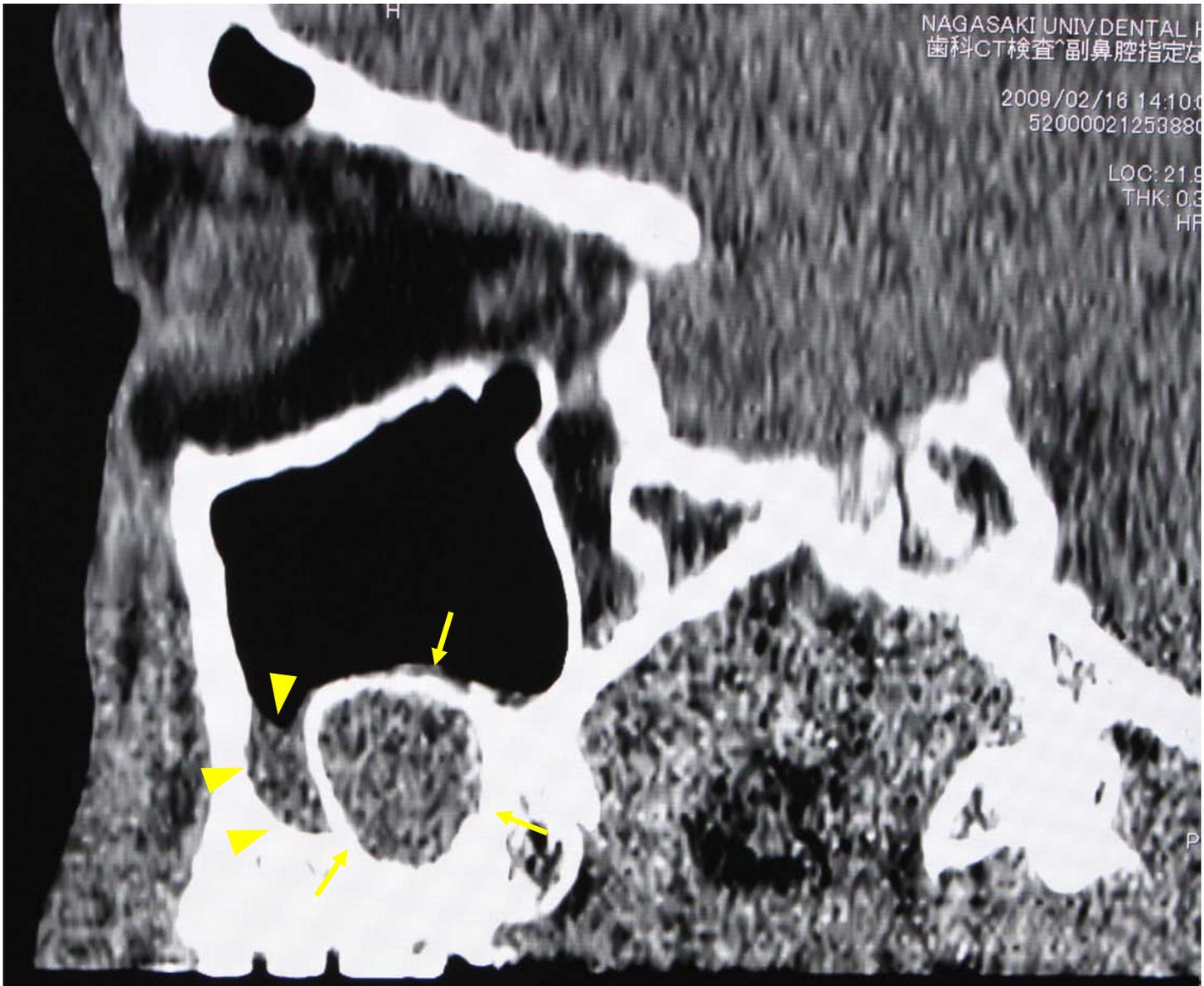


Fig. 2B

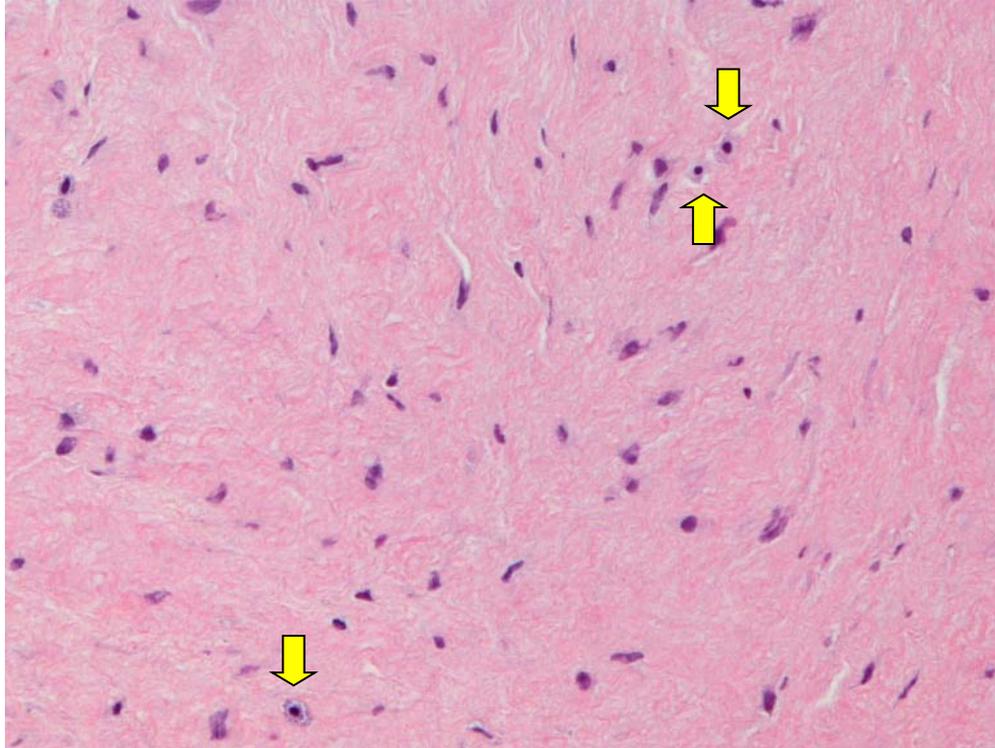


Fig. 3

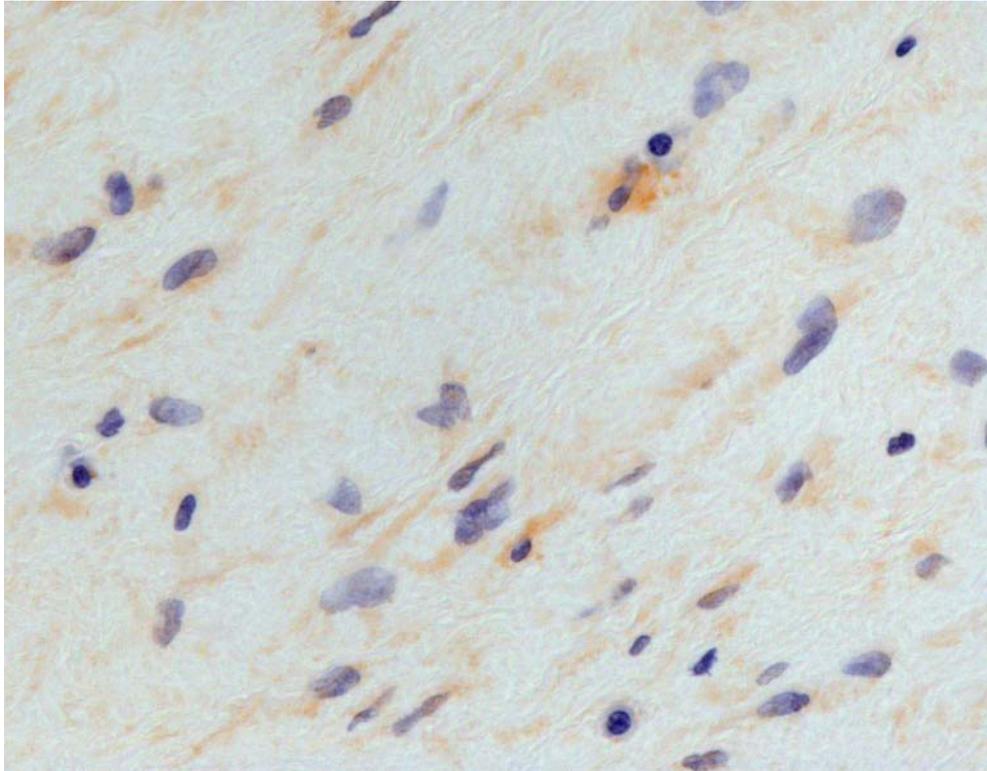


Fig. 4

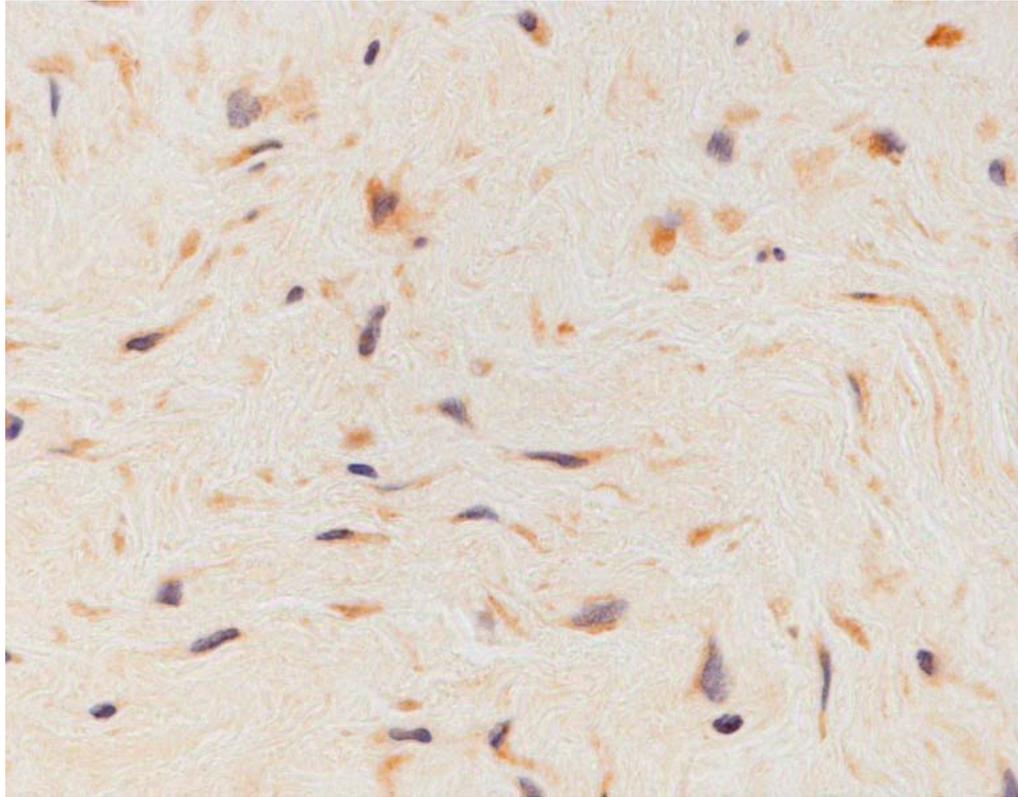


Fig. 5

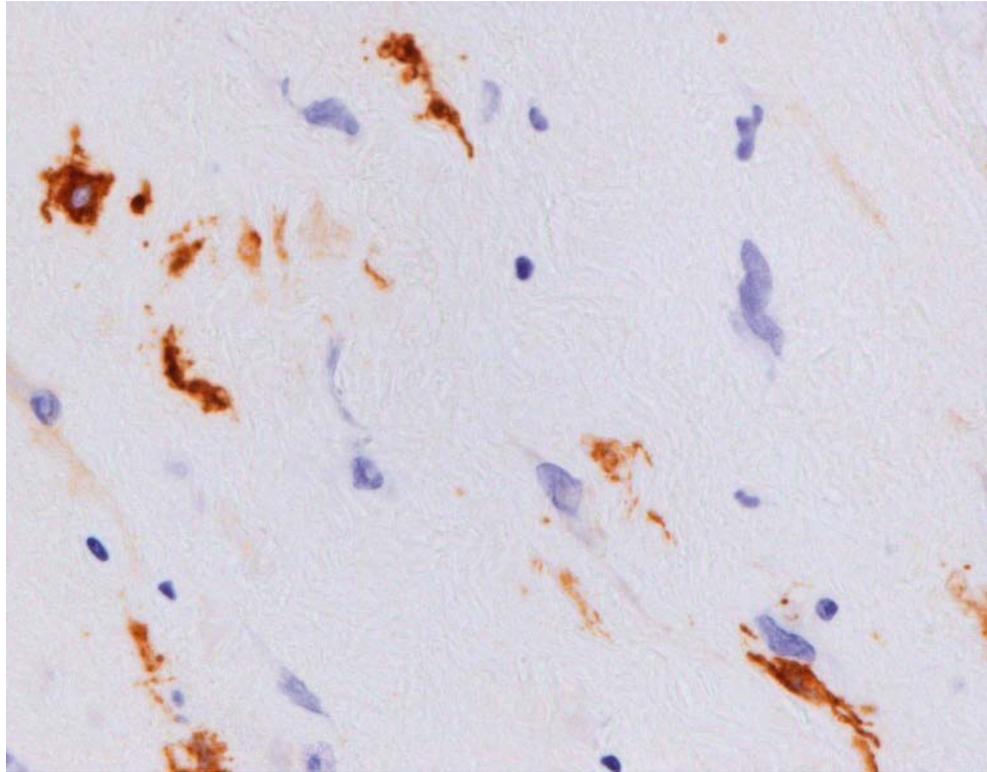


Fig. 6