CASE REPORT

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Cystic lymphangioma of nasopharynx in a 54-year-old man – case report. A new histogenetic hypothesis

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Abstract

Lymphangiomas are enough rare benign congenital tumors of the lymphatic vessels, frequently encountered during childhood. They are found in the head and neck region, the isolated localization in the nasopharynx is very rare. We present the case of 54-year-old man admitted in the Department of Ear, Nose and Throat (ENT), Emergency University Hospital of Bucharest, Romania, with a nasopharynx tumor certificated by computed tomography (CT) scan with significant bleeding to a previous incisional biopsy temptation rising angiofibroma suspicion. We performed the radical surgical excision of mass by transoral approach. Postoperative bleeding imposed angiography with right internal maxillary artery embolization. Histopathological evaluation showed the diagnosis of lymphangioma. After three years, the patient is without recurrence.

Keywords: nasopharyngeal lymphangioma, surgery, transoral retrovellar approach, histopathology.

Introduction

Lymphangiomas are a rare benign congenital malformations of the lymphatic vessels, frequently encountered during childhood. Almost 90% of lesions are diagnosed before two years of age, the onset of the lesion after two years of age being rare [1]. The cases diagnosed and treated in adults are rare as they are reported in literature. Lymphangiomas are rare tumors, representing about 4% of all vascular tumors and 25% of children's benign vascular tumors [2].

Lymphangiomas may develop in any organ, but about 75% appear in the head and neck [2–4]. Most of the cases occur in the skin of head and neck region and the most commune sites are submandibular region and parotid region [1, 5, 6].

Isolated localization of lymphangioma in the nasopharynx is very rare. We found a small number of cases for nasopharyngeal cystic lymphangioma in literature: we found two cases that had been reported in Russia, in 1966 and 1969 [7]; other in Japan, in 1990 [8]; three others in India in 2013, 2014 and 2016 [7, 9]. Therefore, lymphangioma arising in the nasopharynx in an adult is very rare.

The symptoms are non-specific and that is why there may be confusions regarding diagnosis (especially in adults) with various other malignant or benign tumors [10–12]. The histopathological (HP) aspects are the ones that confirm the diagnosis of the lesion.

We present an extremely rare case (according to our knowledge, the first case with nasopharyngeal localization published in Romania) of a lymphangioma in an adult, which raised problems of both positive and differential diagnosis.

Case presentation

We will present the case of a 54-year-old man with bilateral nasal obstruction syndrome over six months who was diagnosed in another Ear, Nose and Throat (ENT) Service with nasopharyngeal tumor. The biopsy attempt had been complicated with a severe nasal bleeding with posterior package for five days, rising the suspicion of angiofibroma. The histopathology exam of the bioptic fragment indicated mixed fibrohemangioma. After six months, the patient was admitted in ENT Compartment, Emergency University Hospital of Bucharest, Romania. The ENT examination and fibroscopy revealed in nasopharynx an encapsulated, pulsatile round tumor, with pericapsular vascularization on dorsal face of uvulae with bilateral obliteration of choanae.

Radiography of anterior sinuses revealed the projection of a round tumor on nasopharyngeal area (Figure 1). A contrast-enhanced computed tomography (CECT) of neck reported an intense enhancing soft tissue mass measuring 20/22 mm in axial section and 22 mm in coronal section, projected on dorsal face of uvulae with a thin aeric space

between the mass and the posterior and superior wall of nasopharynx; the cranial extension blocked both choanae especially the right one and the caudal extension is near right tonsillar fossa (Figure 2, a and b).

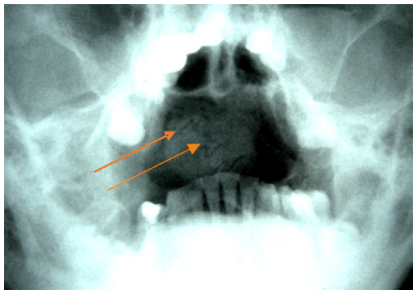

Figure 1 – ***X-ray of anterior sinuses showing the tumor projection on nasopharyngeal area with significant vascular drawing.***

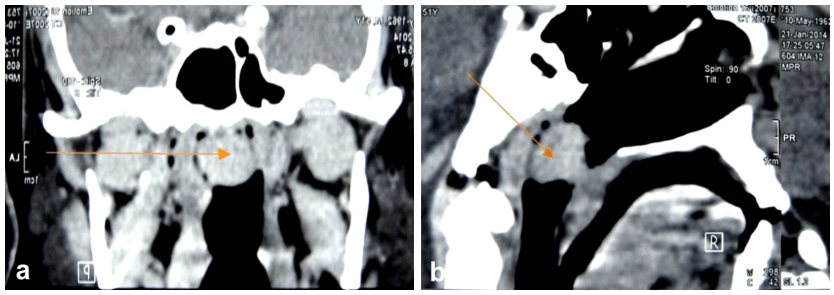

Figure 2 – ***(a and b) CT scan showing mass in nasopharynx arising from dorsal face of uvulae.***

Bilateral carotid angiography showed a fine tumor blush from right external carotid artery without a typical aspect for angiofibroma of nasopharynx (Figure 3).

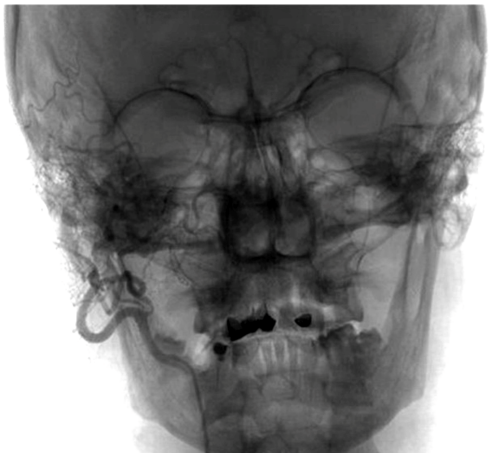

Figure 3 – ***Right carotid angiography showing a fine tumor blush from external carotid artery.***

After routine blood investigations, preanesthetic check-up and informed written consent, patient was prepared for surgery. The surgery was under general anesthesia and we were prepared with blood substitution products in case of bleeding. We used the transoral retrovellar approach. We made the retraction of soft palate with Nelaton catheters inserted through nostrils for better visualization and we put posterior package on them in waiting. We realized the radical ablation of the tumor by Brunnings forceps type an after that, a bilateral a posterior package by retraction of Nelaton catheters from oropharynx. The surgical bleeding was about 100 mL. We attempted to take out the posterior package after 48 hours in safety conditions into operation room. We have had an important arterial bleeding (about 200 mL), which imposed right posterior package again. The patient received a re-suspended erythrocyte concentrate international unit and remained under antibiotic treatment (Ceftriaxone 1 g i.v. every 12 hours). We decided after 24 hours to repeat carotid angiography with embolization of right internal maxillary artery in the Department of Interventional Radiology from our Hospital (Figure 4). We took out the posterior package after five days without bleeding. The patient was discharged after 10 days, surgical cured.

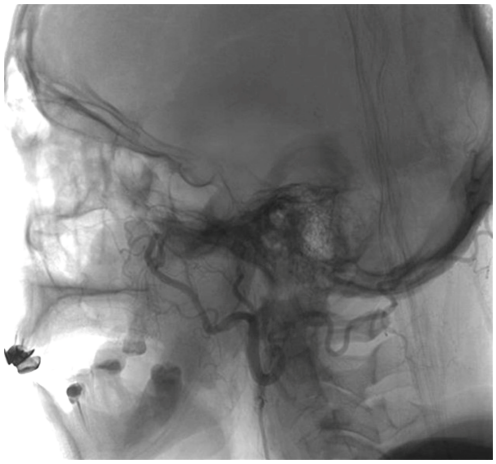

Figure 4 – ***Carotid angiography after right internal maxillary artery embolization.***

The surgical specimen has been sent to the Department of Pathology from our Hospital with previous diagnosis of hemangioma. The pathologist described an encapsulated, yellowish elastic tumor having 25/15 mm. The tissues were routinely fixed in 10% neutral buffered formalin, paraffin embedded and then stained with Hematoxylin–Eosin (HE) and the Goldner–Szekely (GS) green light trichrome. For establishing the positive and differential diagnosis, there were used the following immunohisto-chemical (IHC) markers: anti-CD34 (monoclonal mouse anti-human CD34 Class II, clone QBEnd/10, 1:50 dilution, Dako); anti-CD31 (monoclonal mouse anti-human CD31, endothelial cell, clone JC70A, 1:50 dilution, Dako); anti-FVIII (monoclonal mouse anti-human von Willebrand factor, clone F8/86, 1:50 dilution, Dako); anti-D2-40 (monoclonal mouse anti-human D2-40, clone D2-40, 1:100 dilution, Dako); anti-alpha-smooth muscle actin (α-SMA) (monoclonal mouse anti-human SMA, clone 1A4, 1:100 dilution, Dako); anti-vimentin (monoclonal mouse anti-vimentin, clone V9, 1:50 dilution, Dako); anti-CD133 (monoclonal mouse anti-human CD133, clone 3F10, 1:200 dilution, Novus Biologicals); anti-LYVE-1 (rabbit polyclonal IgG, 1:100 dilution, Santa Cruz Biotechnology); anti-Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1:50 dilution, Dako); anti-p53 (monoclonal mouse anti-human p53 protein, clone DO-7, 1:100 dilution, Dako).

The HP study highlighted the presence of cystic structures, communicating between them, paved with a

vascular endothelium, full of eosinophil liquid, rich in proteins and rare lymphocytes (Figure 5, a and b). In the wall of cystic formations, the endothelial cells were frequently doubled by one or more lines of smooth muscular fibers (Figure 6). The aspect and size of cysts were quite varied, in some areas being highlighted only lymphatic capillary structures (Figure 7).

The tumoral stroma was heterogeneous, mainly formed of lax conjunctive tissue. In some areas, the stroma had a myxoid aspect (Figure 8), while in other areas, it was rich in fibers or fibroblast cells (Figure 9). At the tumor periphery, there was highlighted the presence of a cellular and fibrillar densification, thus giving the impression of a pseudocapsule (Figure 10).

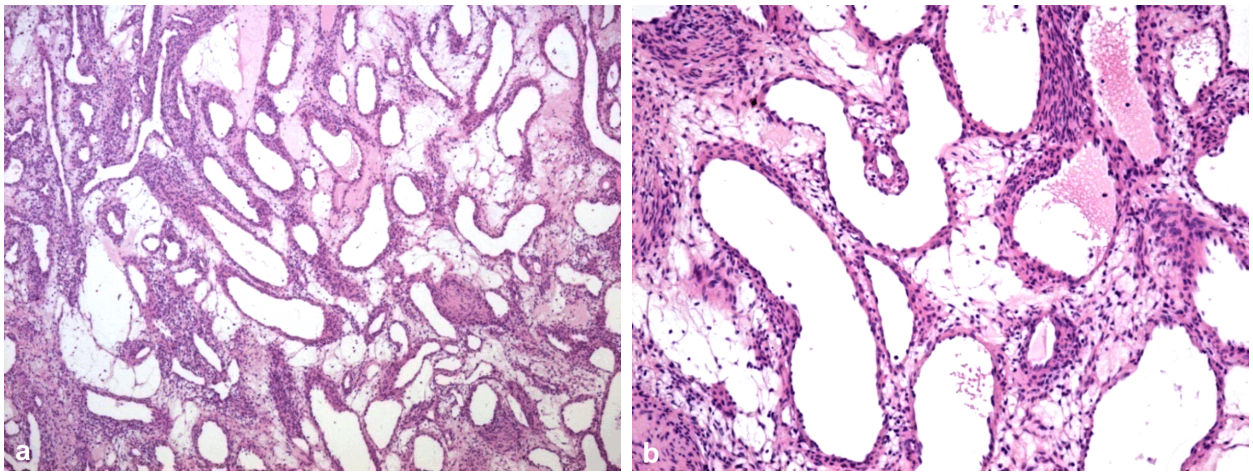

Figure 5 – ***(a) Overall image of the tumor, where there are highlighted numerous microcystic structures; (b) Detail from previous image. HE staining: (a) ×40; (b) ×100.***

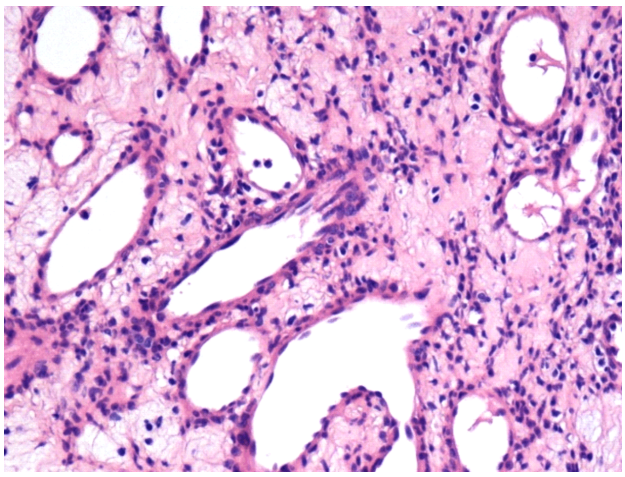

Figure 6 – ***Cystic formations with the wall formed of various lines of cells (HE staining, ×200).***

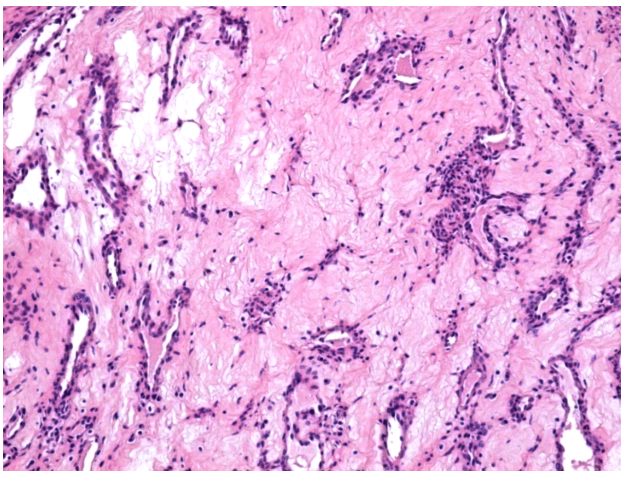

Figure 7 – ***Tumoral area with numerous lymphatic capillary structures, arranged in a lax stroma (HE staining, ×100).***

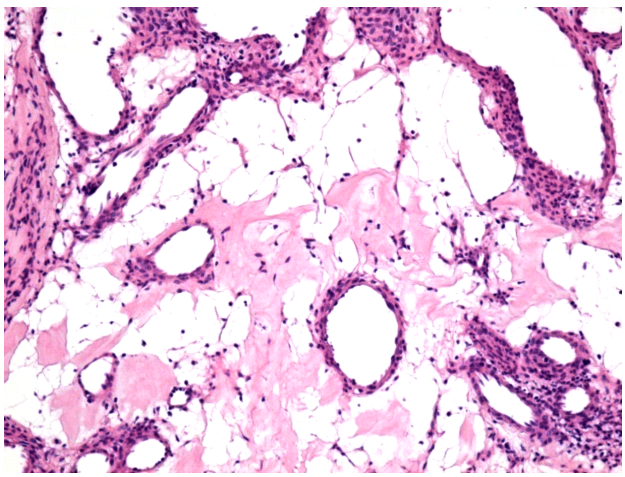

Figure 8 – ***Tumoral stroma of myxoid type (HE staining, ×100).***

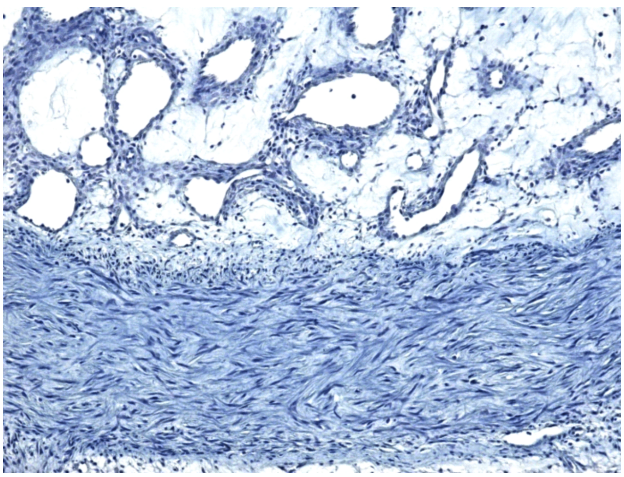

Figure 9 – ***Area of tumoral stroma rich in fibroblast cells (GS trichrome staining, ×100).***

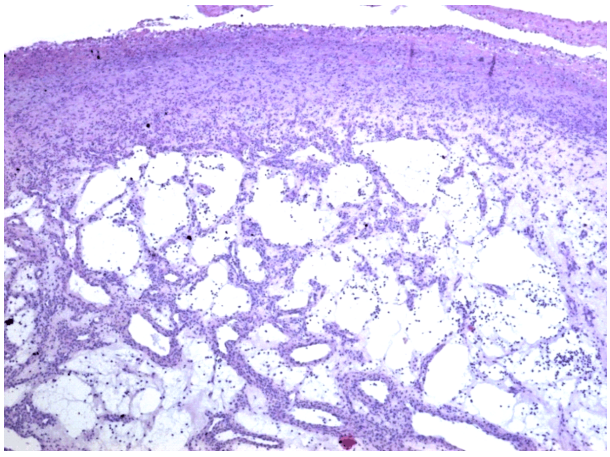

Figure 10 – ***Image from the tumor periphery, where there may be observed the presence of a dense structure with a pseudocapsule aspect (GS trichrome staining, ×40).***

The IHC examination showed that the endothelial cells that paved the cystic cavities were positive to the anti-CD34, anti-CD31, anti-FVIII (von Willebrand) antibodies and negative to the anti-D2-40 antibody (Figure 11, a and b).

The immunomarking with anti-*α*-SMA antibody showed that the wall of the cystic formations was made of a line of endothelial cells positive to this antibody and one or more lines of fusiform cells (probably smooth muscle cells), also positive to the anti-*α*-SMA antibody (Figure 12a). Also, in the stroma, there were identified, isolated or grouped numerous fusiform cells positive to the anti-*α*-SMA antibody, possibly myofibroblasts or smooth muscle fibers (Figure 12b). The vimentin immunostaining showed that both endothelial cells and some stromal cells were intensely positive to this antibody (Figure 13, a and b). Also, the endothelial cells were intensely positive to anti-CD133 and anti-LYVE-1 antibodies (Figures 14 and 15).

For evaluating the tumoral aggressiveness and for estimating the proliferation index of the endothelial and stromal cells, we marked the tumor sections with the anti-Ki67 antibody. We observed that less than 3% of the tumor cell nuclei were positive to this antibody (Figure 16), which shows a reduced proliferation index.

Starting from the idea that some tumoral cells present genetic changes, we investigated the changes of *TP53* gene, by using the anti-p53 antibody. As it may be seen in Figure 17, more than 30% of the endothelial cells and stromal cells were positive to the anti-p53 antibody, which shows the emergence of pathological p53 proteins because of *TP53* gene alteration.

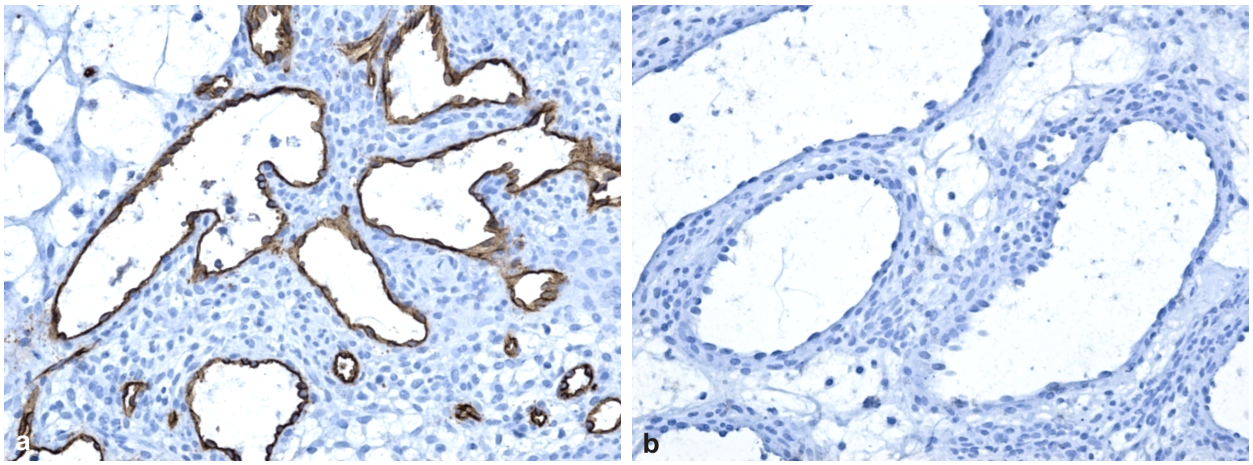

Figure 11 – ***(a) Cystic cavities paved with endothelial cells positive to anti-CD34 antibody (Anti-CD34 antibody immunostaining, ×200); (b) Cystic cavities with an endothelium negative to anti-D2-40 antibody (Anti-D2-40 antibody immunostaining, ×200).***

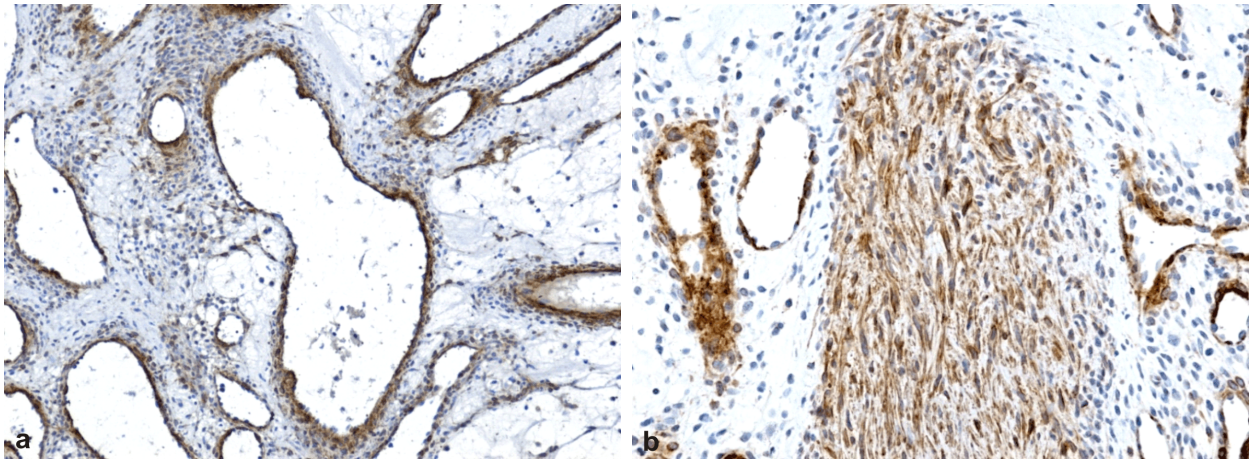

Figure 12 – ***(a) Cystic cavities paved with endothelial cells, doubled by fusiform cells (most probably myocytes) positive to anti-α-SMA antibody; (b) Stromal cells positive to anti-α-SMA antibody. Anti-α-SMA antibody immunostaining: (a) ×100; (b) ×200.***

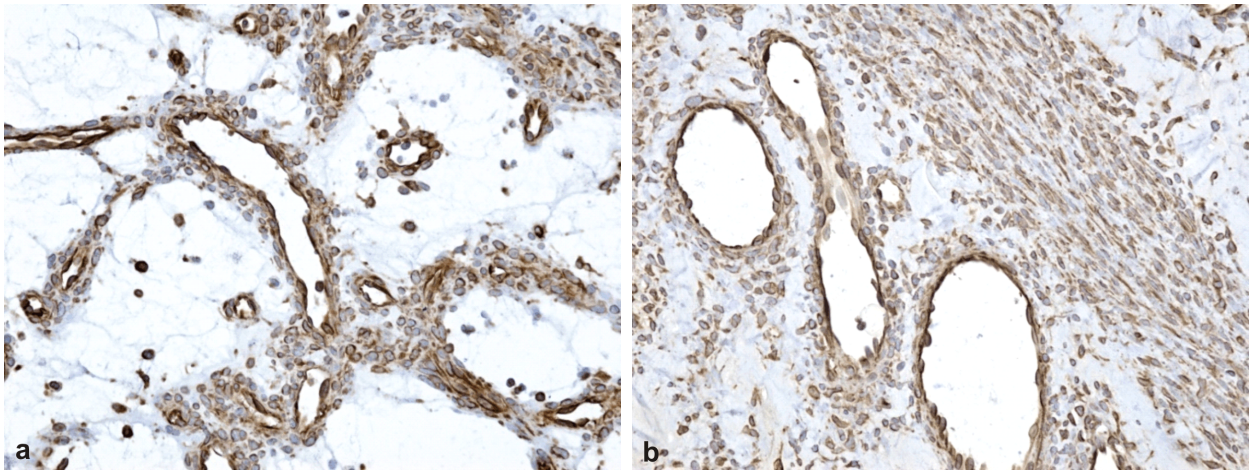

Figure 13 – ***(a) Endothelial cells intensely positive to vimentin; (b) Intensely positive reaction of the cells from the wall of cystic cavities, and of some stromal cells, to vimentin. Anti-vimentin antibody immunostaining: (a and b) ×200.***

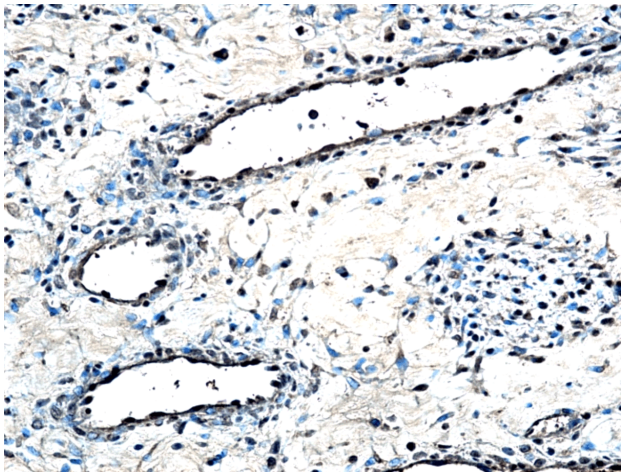

Figure 14 – ***Endothelial and stromal cells positive to anti-CD133 antibody (Anti-CD133 antibody immuno-staining, ×200).***

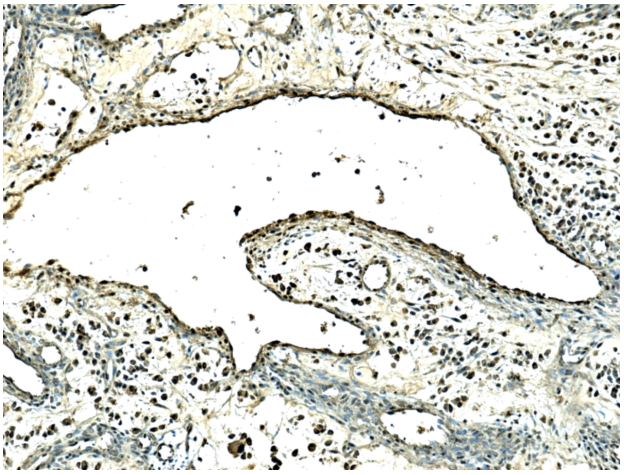

Figure 15 – ***Cystic cavities differentiated by an anti-LYVE-1 antibody positive endothelium (Anti-LYVE-1 antibody immunostaining, ×100).***

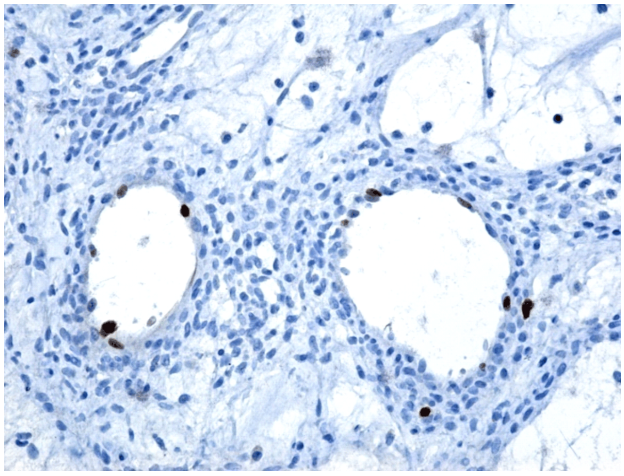

Figure 16 – ***Rare endothelial and stromal cells positive to anti-Ki67 antibody (Anti-Ki67 antibody immunostaining, ×200).***

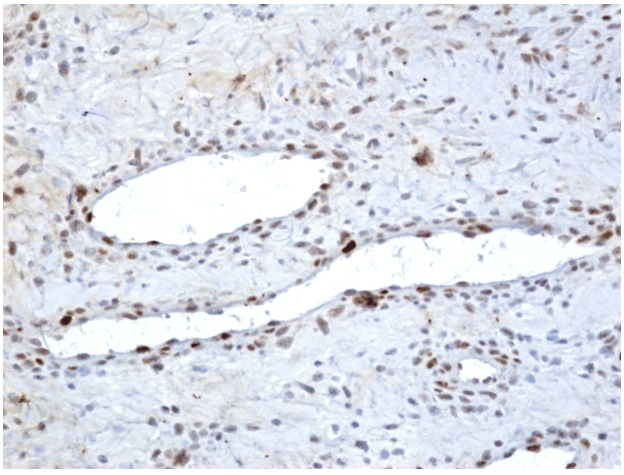

Figure 17 – ***Numerous endothelial and stromal cells positive to p53 (Anti-p53 antibody immunostaining, ×200).***

The HP diagnosis was cystic lymphangioma with complete excision. Follow-up, the evolution of patients was a good one due to the benign nature of the tumor and complete ablation. We checked the patient to 1, 3, 6, 12 months and after that every year for two years and he was recurrence-free.

Discussions

Lymphangiomas are considered to be congenital malformations of lymphatic vessels present at birth, with 80–90% detected by the second year of life. About 75% of cases involve the skin of head and neck region.

Submandibular and parotid regions are the most common sites [1]. Some authors [13], by evaluating the anatomical distribution of head and neck lymphangiomas in children, observed that the most affected area was the submandibular one (37%), followed by the parotid glands (31%). Other studies showed that lymphatic malformations of the head and neck had an incidence of 1.2–2.8 in 1000 births [6]. Most studies considered that these malformations are the result of an abnormal development of embryonic lymphatic vessels or of these structures failure to connect to the local venous or lymphatic system [14]. Other authors consider that these tumors have their origin in the debris of embryonic lymphatic tissue, isolated in some areas, which preserved their growth potential [3, 15].

Lymphangiomas are benign slow growing tumors. Naidu & McCalla [16] reported a comprehensive review of studies on lymphatic malformation in adults between the years 1828 and 2000. They found 91 adult cases of lymphangiomas, located on the head and neck. Although over 90% of lymphangiomas are congenital, later presentation may occur because of trauma, infection, neoplasms or iatrogenic injuries [7].

Apparently, our patient had none of favorable factors, except previous biopsy. Primary lymphangiomas of the pharynx are very rare. Our adult male patient had a lymphangioma of nasopharynx, which is an unusual site and an unusual age for onset.

Lymphangiomas are divided in microcystic, macrocystic and cystic hygromas, according to the size of the lymphatic vessels [5, 9, 17]. Microcystic lymphangiomas are composed of small, thin walled, capillary-sized lymphatic vessels and are located in the epidermis. Macrocystic (cavernous) lymphangiomas are common and they are composed of dilated lymphatic vessels. Cystic lymphangiomas (cystic hygromas) are large lymphangiomas filled with straw-colored, protein-rich fluid [5]. The literature describes, also, hemangiolymphangiomas, which are lymphangiomas with a vascular component; both lymphangioma and hemangioma of nasopharynx are rare in adults. We believed that our case is more a hemangiolymphangioma-like because of recurrence of bleeding, a very rare pathology of the nasopharynx in adults.

Microcystic lymphangiomas contain cysts, each of which measures less than 2 cm^3, macrocystic lymphangiomas contain cysts measuring more than 2 cm^3; mixed lymphangiomas contain both microcystic and macrocystic components [5].

Symptoms are usually nonspecific for nasopharyngeal localization, including nasal obstruction, obstruction of Eustachian tube with serous otitis, nasal bleeding and some type of dysphagia or speech difficulties if the lesion grows [17].

Positive diagnosis imposes nasal fibroscopy for direct visualization and high performance imagistic [CECT scan or magnetic resonance imaging (MRI)] to establish the local extension of the lesion [3]. The carotid angiography can be useful to identify a tumor vascularization of angiofibroma type and allows selective embolization to diminish perioperative bleeding. We considered that biopsy to be prohibited in a pseudoencapsulated tumor of nasopharynx because of the high risk of bleeding. Histopathology and immunohistochemistry make the certitude diagnosis.

Other benign masses of nasopharynx as angiofibroma, antrochoanal polyps, nasopharyngeal teratoma, cystic lesions, should be included in the differential diagnosis for a delimited tumor of nasopharynx [7, 9–11]. We cannot exclude a teratoma [18], a lymphoma or a nasopharyngeal carcinoma until histopathology [19].

In our case, the HP and IHC examinations allowed establishing the diagnosis and highlighted some particular microscopic aspects.

As it may be observed from our images, histopathologically speaking, lymphangiomas consist of multiple, intertwining lymph vessels in a loose fibrovascular stroma. The size and shape of these vessels was extremely varied. In our case, there were identified microcystic structures, together with structures with reduced lumen, of the lymphatic capillary type.

We found many theories to explain the apparition of lymphangiomas. A theory sustain the blockage of normal growth of the primitive lymph channels during embryogenesis, another theory that the primitive lymphatic sac does not reach the venous system; the third theory sustain that lymphatic tissues lays in the wrong area, during embryogenesis [1]. In adult lymphangiomas may appear secondary to induction of dormant rests of embryonic lymphatic tissue by an infection, a tumor or by a trauma [17].

The IHC study performed by us showed that both endothelial cells and the stromal ones presented some particular characteristics. Thus, the endothelial cells were negative to the D2-40 monoclonal antibody and positive to CD31, CD34 and FVIII (von Willebrand) antibodies. For us, there was a surprise to observe that lymphatic endothelial cells were not marked by the anti-D2-40 antibody that is known as the most specific and more sensitive marker for detecting lymphatic vessels and it is used on a large scale for the tissues included in paraffin, either normal or pathological [20–23]. Also, the lymphatic cells of the endothelium were positive to anti-α-SMA, anti-vimentin, anti-CD44, anti-CD105, anti-CD133, anti-LYVE-1 antibodies and were negative to anti-CD117 antibody.

The intense positive reaction of the endothelial cells to anti-α-SMA antibody shows the presence of alpha-actin filaments in their cytoskeleton. Moreover, the IHC reactivity similar to that of stromal myofibroblasts makes us consider that the endothelial cells that covered microcystic cavities of the lymphangioma were formed from myofibroblasts through a process of mesenchymal–endothelial transition.

Some authors (Ubil *et al.*, 2014) showed that fibroblasts, considered mature cells, in certain stress conditions, may generate new endothelial cells and blood vessels, through a mesenchymal–endothelial transition process, having an identical functional similitude with the one of native endothelial cells [24]. Also, the same authors showed that p53 protein is synthesized in large quantities in conditions of cellular stress and it is involved in the mesenchymal–endothelial transition process. We identified numerous endothelial and stromal cells positive to anti-

p53 antibody, which confirms some theories released by Ubil *et al.* (2014) [24].

In our study, lymphatic endothelial cells were positive to the anti-vimentin antibody, similar to many other stromal cells, which shows the common mesenchymal origin of endothelial lymphatic cells and stromal cells.

Vimentin is a structural protein that belongs to type III proteins from the intermediary filaments of the cytoskeleton [25]. It is present in the mesenchymal cells, where it forms the network of cytoskeletal filaments that extend from the nucleus periphery to the cellular membrane, thus giving a mechanical strength to cells [26]. Although this structural role was considered the main role played by vimentin for a long time, now it is clear that interferes with the adherence and migration processes of cells, as well as in the cellular signaling [27–29]. Also, vimentin is an essential marker of the epithelial–mesenchymal transition process [30].

The positive reaction of the lymphatic endothelium cells to anti-CD133 antibody makes us believe that these cells may have their origin in the mesenchymal stem cells in the bone marrow. Various studies showed that mesenchymal stem cells may migrate and may be involved in the lymphangiogenesis processes in pathological conditions [31, 32].

We consider that the etiopathogenic mechanism of lymphangiomas in adults may be different from that in children. In some situations, local or bone marrow mesenchymal stem cells may migrate, proliferate and generate new lymphatic vessels, through a mesenchymal–endothelial transformation.

We consider that nasopharyngeal lymphangiomas, without treatment, can be infected, can cause hemorrhage and a mass effect associated with rapid growth of the lesion with exteriorization in oropharynx [5]. Nasal respiration difficulties, recurrent to permanent conductive hearing loss, swallowing problems might be present due to mass effect.

Treatment for nasopharyngeal lymphangiomas is surgical resection, which still remains the gold standard [5, 7, 9]. We can use transoral, endoscopic or combined approaches. The transoral approach can be retrovellar or transvellar, depending on tumor size [33–35]. We excised the lesion, in our case, under direct vision, by transoral retrovellar approach. This limited the risk of injury to the surrounding organs.

Conclusions

We report a case of nasopharyngeal lymphangioma in a 54-year-old man, because of the rare site of origin and unusual age of presentation. It is important to make a differential diagnosis with nasopharyngeal angiofibroma, regarding long-term prognosis. Bilateral carotid angiography may guide the diagnosis and allows preoperative embolization diminishing surgical bleeding. We consider that the incisional biopsy is prohibited, and radical surgery is the only way for cure. The HP evaluation revealed the final diagnosis. We consider that the etiopathogenic mechanisms of lymphangiomas diagnosed in adults may be different from these diagnosed in children.

Ethical approval

All authors hereby declare that all experiments have been examined and approved by the appropriate Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of interests

Authors have declared that no conflict of interests exists.

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