

CASE REPORT

Oncocytic cyst of the larynx: an unusual occurrence

Insolita occorrenza di cisti oncocitica della laringe

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SUMMARY

Oncocytic cysts of the larynx are rare benign, slow growing lesions that are lined predominantly or exclusively by oncocytes, the cytoplasm of which contains a considerable number of hypertrophied mitochondria, which accounts for their eosinophilia and swollen appearance. The oncocytic change is a phenomenon of metaplasia which occurs frequently in epithelial endocrine cells with high metabolic activity and it is also associated with inflammation, degenerative process or cellular ageing. In the larynx, oncocytic metaplasia is very uncommon, but it is occasionally seen in the lining of laryngeal cysts, which are found most commonly in the ventricles or in the false vocal cords, where seromucinous glands are more abundant. Oncocytic cysts typically occur in the elderly and are usually solitary, with involvement of an isolated site, whereas diffuse involvement with multiple cysts is extremely rare. Hoarseness is the most common presenting symptom, while pain, stridor or laryngeal obstruction are unusual complaints. Management of these lesions is conservative and consists of local excision, endoscopic removal being the treatment of choice. Although oncocytic cysts are benign lesions, follow-up is recommended, as recurrence is possible, especially in the case of patients with multiple involvement, since they may show a tendency to develop new cysts. To date, approximately 150 cases of laryngeal oncocytic cysts have been published. Herein, a very unusual case is presented occurring in a 43-year-old male patient, therefore, "epidemiologically" atypical for developing oncocytic lesions. Causes of oncocytic changes and pathogenesis of laryngeal cysts are discussed.

KEY WORDS: Larynx • Laryngeal cysts • Oncocytes

RIASSUNTO

Le cisti oncocitiche della laringe sono lesioni benigne rare, rivestite del tutto o in prevalenza da oncociti, larghe cellule poligonali che devono la loro apparenza rigonfia e la eosinofilia al notevole contenuto citoplasmatico di mitocondri ipertrofici. La trasformazione oncocitaria è un fenomeno di metaplasia che si verifica di frequente nelle cellule endocrine con elevata attività metabolica, ma è anche associata a processi infiammatori, degenerativi e d'invecchiamento. Nella laringe la metaplasia oncocitaria è molto rara, verificandosi occasionalmente nell'epitelio di rivestimento delle cisti localizzate più comunemente nel ventricolo o sulla falsa corda, dove maggiore è l'abbondanza di ghiandole sieromucose. È una patologia tipica dei soggetti anziani, generalmente ad occorrenza solitaria, mentre rara è l'evenienza di localizzazioni multiple. La disfonia è il sintomo di presentazione più comune, più di rado dolenzia, stridor o dispnea. Il trattamento di elezione delle cisti oncocitiche è l'escissione endoscopica, preferibilmente mediante laser a CO₂. Sebbene si tratti di lesioni benigne, si raccomanda il follow-up, specie nei casi con localizzazioni multiple, che possono avere tendenza a recidivare. In letteratura sono state riportate a tutt'ora circa 150 casi di cisti oncocitiche laringee. Alla luce del caso presentato, particolarmente insolito per l'età del paziente (43 anni, quindi, epidemiologicamente atipica), vengono discussi i possibili meccanismi responsabili della trasformazione oncocitaria e la patogenesi delle cisti oncocitarie laringee.

PAROLE CHIAVE: Laringe • Cisti laringee • Oncociti

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Introduction

Oncocytic cysts of the larynx are rare benign, slow-growing lesions, lined predominantly or exclusively by oncocytes, large polygonal cells with hyperchromatic, often bizarre, nuclei and an eosinophilic granular cytoplasm. This peculiar aspect of the cytoplasm is related to the presence of a considerable number of hypertrophied mitochondria, accounting for the eosinophilia of the cells and for the swollen appearance of the oncocytes¹. The oncocytic change is a phenomenon of metaplasia which occurs frequently in

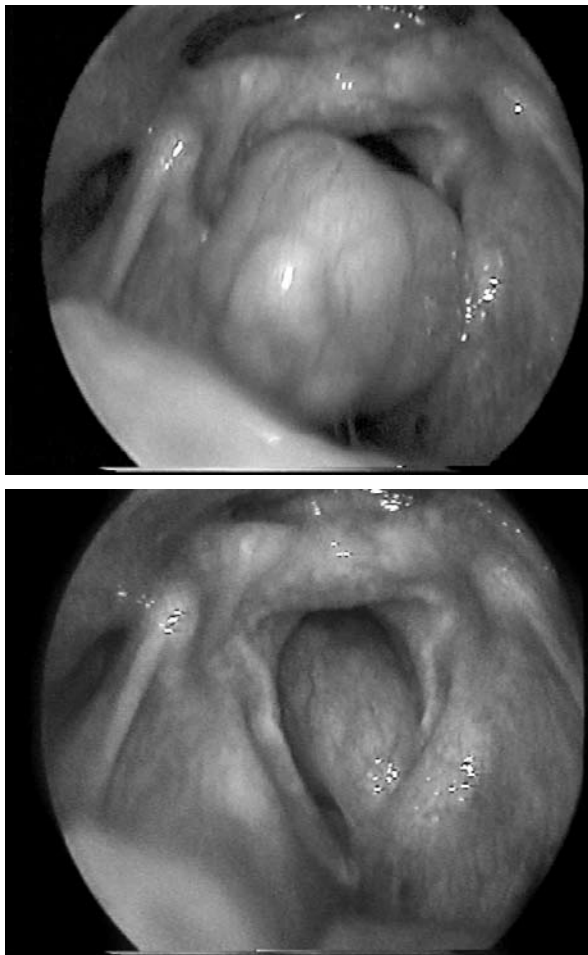
epithelial endocrine cells with high metabolic activity and it is also associated with inflammation, degenerative processes or cellular ageing². Since their original description, oncocytes have been identified within the epithelial lining of the glands and mucosa of the upper respiratory tract, the tongue, pharynx and oesophagus, the gall-bladder, and in the lacrimal and salivary glands, as well as within the parenchyma of the hypophysis, thyroid, liver, pancreas, internal genitalia, adrenals, kidney, thymus, breast and parathyroids. The significance in the occurrence of these cells, in such a variety of locations, is not known. In the larynx, oncocytic

metaplasia is very uncommon, but it is occasionally seen in the lining of laryngeal cysts, which are most commonly found in the ventricles or in the false vocal cords, where seromucinous glands are more abundant. However, oncocytic cysts can occur anywhere in the larynx, except the free edge of the true vocal cord, which is devoid of glandular epithelium. They are usually solitary, with involvement of an isolated site, whereas diffuse involvement with multiple cysts is extremely rare³. These cysts typically occur in the elderly (most patients are ≥ 70 or ≥ 80 years of age) and their incidence in laryngeal biopsies is between 0.5% and 1%⁴. To date, approximately 150 cases of laryngeal oncocytic cysts have been described in the literature⁵⁻⁹.

The present report refers to a very unusual case occurring in a male patient in his early forties.

Case report

A 43-year-old male, who had smoked 40 cigarettes a day for more than 20 years, presented with severe dysphonia and mild inspiratory stridor. The patient's medical history was unremarkable and his social behaviour was notable for sustained vocal strain. He reported no dysphagia, odynophagia, otalgia, cough or haemoptysis, only hoarseness and mild shortness of breath gradually worsening after an attack of "flu". Direct laryngoscopic examination with rigid endoscope revealed a huge pedunculated polypoid mass, arising from the inferior aspect of the left false



Figs. 1 a, b. Direct laryngoscopic view of cyst during breathing.



Fig. 2. Pre-operative CT scan showing a supraglottic mass isodense to the surrounding soft tissue.

cord and covered with normal-looking mucosa. The lesion almost totally occluded the glottis on inspiration (Fig. 1 a, b). The true vocal cords were normal in appearance and mobility. The remainder of the head and neck examination did not disclose any other abnormalities. Computed tomography showed this mass to be cystic in nature, filled with a liquid of the same density as the surrounding tissues (Fig. 2). Under direct suspension laryngoscopy, the lesion was completely excised using CO₂ laser. The mass measured 2 x 1.8 x 1 cm, had a smooth pink surface and, when opened, disclosed gelatinous contents (Fig. 3). The lesion was sent for histological analysis and was found to be a laryngeal cyst with papillary oncocytic changes. At one-year-follow-up, there was no evidence of recurrence, and the patient's voice had returned to normal.

Histological findings

A fresh specimen was fixed in 10% neutral buffered formaldehyde solution for 24 hours. Macroscopic examination of the specimen was carried out and cross sections were obtained. Paraffin blocks, 5 mm thick, were prepared;

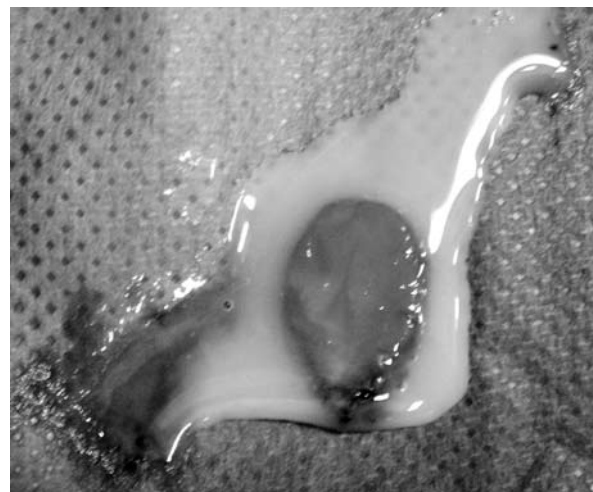


Fig. 3. Cyst was filled with mucoid, gelatinous material.

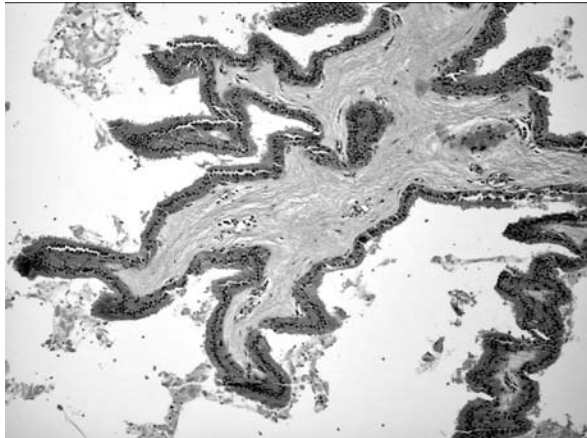


Fig. 4. Papillary infoldings in mono-stratified oncocytic epithelium (H&E, original magnification 100xHPF).

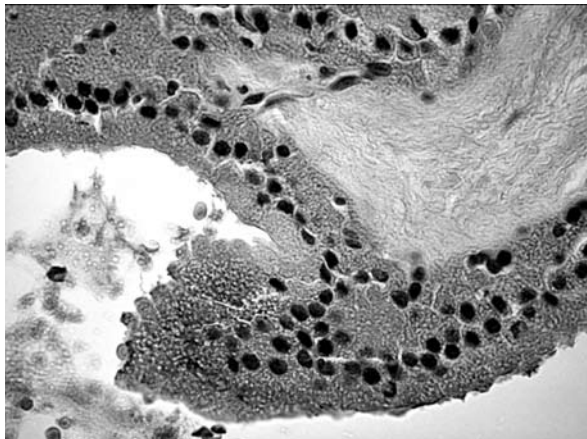


Fig. 5. Oncocytic epithelium composed of columnar cells with darkly stained nuclei and abundant granular, eosinophilic cytoplasm (H&E, original magnification 400xHPF).

thereafter, 4 μ m sections from each block were stained with haematoxylin-eosin (HE). Histological examination revealed a cyst filled with mucoid material, with papillary infoldings lined with a monostratified oncocytic epithelium (Fig. 4). Oncocytes were composed of columnar cells with darkly stained nuclei and abundant granular, eosinophilic cytoplasm without atypia or mitotic activity (Fig. 5). The surface of the cyst was covered by a normal stratified squamous epithelium. The cyst was localized in the lamina propria, which was composed of connective tissue, rich in blood vessels, and with rare lymphoid elements.

Discussion

Laryngeal oncocytic cysts are uncommon lesions, found predominantly in females^{4,10} and at a mean age of over 60 years^{5,6,11}. Yamase and Putman¹² observed that 80% of larynges from patients over the age of 50 years showed focal oncocytic changes, while these changes were absent in the larynx of patients under 50 years of age. However, oncocytic lesions have occasionally been found in subjects under 50 years of age and, exceptionally, in very young patients⁵. Hoarseness is the most common presenting symptom, persisting for weeks or even years before the diagnosis

is made. Pain, stridor or laryngeal obstructions are unusual complaints. Management of these lesions is conservative and consists of local excision, the endoscopic approach being the treatment of choice. Although oncocytic cysts are benign lesions, follow-up is recommended, as recurrence is possible, especially in the case of patients with multiple involvement, since they may present a tendency to develop new cysts¹¹. In these cases, multifocal oncocytic metaplasia is probably more common than currently held and is likely responsible for "recurrence". There have been no definite reports of malignant transformation of oncocytic cysts in the larynx, nevertheless, association with squamous carcinoma of the larynx has been reported⁵. A review of the literature demonstrated that controversy exists concerning the nature of oncocytic cysts of the larynx.

According to some Authors, such as, for instance, Spaun and Olesen¹³, a neoplastic nature is responsible for these cysts (hence the term "oncocytoid papillary cystadenoma"), considering the papillary infoldings seen in these cysts as evidence of the neoplastic nature of the condition.

Others disagree and argue that the papillary infoldings merely represent epithelial hyperplasia rather than neoplasia¹⁴ and suggest that metaplasia and hyperplasia affect the distal segment of a mucinous gland duct, thus the entire proximal segment becomes cystically dilated¹².

For some Authors^{10,11}, oncocytic cysts may represent "retention cysts" of the seromucinous glands of the larynx with oncocytic metaplasia of the lining and their occurrence represents a degenerative process that is aggravated by constant or increased pressure.

What causes oncocytic changes is still under debate, since the exact significance of oncocytes is unknown. Oncocytes are not generally present in young subjects, but are increasingly observed, with advancing age, in the salivary glands and other organs. They are often associated with increased activity of respiratory chain enzymes, including cytochrome c-oxidase and succinate dehydrogenase². Based on the fact the tumours of the thyroid composed of oncocytes are rarely functional¹, it is hypothesized that conversion to an oncocytic appearance is the result of physiological changes related to functional exhaustion. Mitochondrial hyperplasia may be compensatory to the lack of manufacture of one or more of the mitochondrial enzyme systems as the cell ages. Altman¹⁵ suggested that mitochondrial proliferation may represent a compensatory mechanism against mitochondrial defects. The hypothesis is supported by the fact that increases in the number of mitochondria are frequently reported in mitochondrial diseases associated with respiratory chain defects. However, the enhanced histochemical activity of the respiratory chain complexes is not associated with improved cell performance¹⁶ suggesting a defect in the energy-producing machinery of the affected cells. Mounting evidence has linked the presence of oncocytes to the acquired mitochondrial dysfunction¹⁷. Changes in oncocytes are also seen in the hepatocytes of patients receiving highly active antiretroviral therapy (HAART) as a result of mitochondrial damage¹⁸. The effect of the drug on mitochondrial DNA replication leads to depletion of mitochondrial-encoded proteins and configurational defects of the inner membrane of the mitochondria leading to reduced and abnormal cristae, in which the electron transport chain and the elementary bodies are found. This mitochondrial dysfunction results in a compensatory increase in mito-

chondrial biogenesis, which results in oncocytic changes in the hepatocytes. Mitochondrial abnormalities, in particular the accumulation of mitochondrial DNA (mtDNA) mutations, have been proposed as a potential cause of normal ageing. One of the most common mtDNA deletions, i.e., the common 4977-bp deletion, which has been described in oncocytomas, has also been shown to be involved in inflammation and ageing². Tanji et al.¹⁹ demonstrated significant deficiencies of mtDNA and mtDNA-encoded respiratory chain enzymes in hepatic oncocytes observed in various chronic liver diseases, mainly cirrhosis and chronic hepatitis, suggesting that mtDNA depletion plays an important role in hepatocellular oncocytic transformation.

Our case of laryngeal oncocytic cyst is of particular interest not only on account of the size of the lesion, but above

all the age of the patient, who was 43 years old, therefore, "epidemiologically" atypical for the development of oncocytic lesions. Chronic inflammation of the mucosa due to prolonged heavy tobacco smoking could have favoured the occurrence of the oncocytic change of the laryngeal mucosa in our patient. This postulate is also supported by the recent evidence of a strong association between cigarette smoking and the occurrence of Warthin tumour of the salivary gland²⁰, a lesion composed of oncocytic cells containing excessive numbers of mitochondria, which show frequent structural abnormalities and reduced metabolic function, probably as a result of an increase in oxidative stress. Furthermore, excessive vocal efforts, with false and true vocal cord hypertension, could have been additional causative factors in the development of such a voluminous cyst.

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