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Diagnosis and therapeutic management updated on intrathoracic schwannoma

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ABSTRACT

Background: Schwannoma is a benign neoplasm derived from Schwann cells. It is usually located in the intracranial nerves, however intrathoracic presentation is possible, leading to compression of adjacent structures and symptoms. The absence of results from physical examination and the presence of mild symptoms (or absence) common to other diseases makes the diagnosis challenging, usually accomplished through imaging. Treatment consists of surgical resection by thoracotomy or thoracoscopy. This study aimed to review this subject with an emphasis on the diagnostic and therapeutic approaches currently available.

Method: Articles were selected by searching the Scopus, Scielo, PubMed and Web of Science databases using the keywords: schwannoma, neurinoma, neurilemmoma, nerve tissue neoplasm, thoracotomy, thoracoscopy and mediastinal neoplasms.

Results: Intrathoracic schwannoma often presents as asymptomatic and is identified during routine imaging tests. The recommended treatment is surgical resection by thoracoscopy or thoracotomy.

Key words: *Schwannoma, neuroma, neurilemmoma, nerve tissue neoplasm, thoracotomy, thoracoscopy, mediastinal neoplasms*

Introduction

Tumors of neurogenic origin make up 20% of such tumors in adults and 25% in children; the vast majority being benign and classified as tumors originating from nerve cells (ganglioneuroma and neuroblastoma) and nerve sheath tumors (Schwannomas and neurofibromas)[1].

Schwannoma (neurilemmoma) was recognized and identified for the first time in 1910 by Verocay and is defined as a neoplasm exclusively composed of Schwann cells of the nerve sheath, generally affecting sensitive fascicles of the cranial and intercostal nerves [2].

Schwannomas are derived from Schwann cells belonging to the peripheral nervous system with the role

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of producing myelin for axons [3]. They occur in close proximity to the nerve of origin, are grayish encapsulated masses, and can present cystic areas [3]. Schwannomas are usually benign, grow slowly, and can emerge at any age, although they are more common in people over 40 years old, and show no preference for sex or ethnicity [3].

Schwannomas occur most commonly as cranial nerve VIII tumors (acoustic neuroma) [3]. Although they are asymptomatic and are discovered accidentally by imaging tests, when extradural, their most frequent presentation is through tumor masses that can compress surrounding structures, becoming symptomatic in the process, as is the case for schwannomas from intrathoracic organs [3-6]. Most tumors of intrathoracic organs emanate in the posterior mediastinum (posterior paraspinal groove), and only 5.4% arise from the chest wall [7].

These tumors are difficult to diagnose and suspicion of diagnosis is the result of analyzing the format of surgical specimens and cell arrangement and the immunohistochemical detection of the S-100 protein [2].

A mutation of the tumor suppressor gene, NF2, shows a close relationship with the presence of schwannoma [3].

The recommended treatment is surgical resection by thoracotomy or thoracoscopy. In the medical literature, few cases of mediastinal schwannomas exclusively treated by thoracoscopy have been reported [3-6].

Materials and Methods

This review article was based on electronic searches in the PubMed, Scielo, Scopus and Web of Science databases. We collected data from case reports, cohort studies and literary reviews using the keywords "schwannoma", "neuroma", "neurilemmoma", "nerve tissue neoplasm", "thoracotomy", "thoracoscopy" and "mediastinal neoplasms". The method raised the following guiding question: "What are the main results and scientific evidence identified in national and international publications concerning the therapeutic approach to intrathoracic schwannoma?".

During the initial survey, the articles were evaluated by seven researchers (authors) according to the following inclusion criteria: articles published in Portuguese, English or Spanish using the selected keyword combinations between 1969 and 2015 that were readily accessible. After the initial selection of material, articles that existed in multiple databases and that featured other tumors existing in intrathoracic organs unrelated to schwannoma were excluded. The final sample consisted of 47 scientific articles.

Results

Epidemiology

Neurogenic tumors account for approximately 20% of all mediastinal neoplasms in adults and approximately 25% in children. Schwannomas and neurofibromas are neurogenic tumors of the posterior mediastinum [6]. The majority of neurogenic tumors in the posterior mediastinum originate from intrathoracic organs, while only 5.4% grow on the chest wall [8]. Schwannomas typically originate from the extremities, head and neck [9]. Though these tumors occur in adulthood, they are often observed at younger ages [10]. They usually affect people in their thirties and forties, although at present, patient ages range from six to 78 years old and no predilection for sex or ethnicity has been described [6].

Pathology

In general, the intercostal nerve lies between the innermost intercostal and internal intercostal muscles. Additionally, this nerve lies along the subcostal groove together with the intercostal blood vessels. It is known that when a neurilemmoma grows towards the external chest wall, it may be blocked by the bottom edge of the adjacent rib [11].

As a result of this growth, schwannomas that originate from the intercostal nerve can project lumps into the thoracic cavity. It is worth noting that there are two possible forms of growth: tumors that develop within and those outside the thoracic wall [11,12].

The first is the neurilemmoma, which arises from the lateral cutaneous branch of the main intercostal nerve. On the chest wall, the intercostal nerve traverses a subcostal course and provides lateral cutaneous branches around the medial axillary line, passing through the subcutaneous layers prior to and after this line [11].

The second possibility is of an anatomical variation. The intercostal nerve can trace a path away from the subcostal groove, blocking the growth of external neurilemmomas [11].

Schwannomas are a neoplasm emerging from Schwann cells of the nerve sheath that usually affect sensitive fascicles of the cranial and intercostal nerves [12]. Cranial nerve VIII is the most affected. Schwannomas are encapsulated, hard, grayish masses that remain in close proximity to the nerve of origin, and areas of cystic changes and xanthomatosis have been documented.

These tumors present two distinct growth patterns: Antoni A and Antoni B, which can both present multiple degenerative changes, such as nuclear pleomorphism, xanthomatous change and vascular hyalinization with no prognostic differentiation [3]. The growth pattern of cells present in Antoni A regions show elongated fusiform nuclei with cytoplasmic expansions arranged in bundles in areas of moderate-to-high cellularity with minimal stroma matrix; "nuclear-free zones" of expansions are situated between the regions of palisaded nuclei associated with Verocay bodies [12]. The Antoni B growth pattern exhibits thinner cells loosely arranged within microcystic spaces and exhibit myxoid alterations. The cells present minimal cytoplasm, within which thin, ill-defined extensions are seen not arranged into bundles . The material between the cells is highly hydrated and is matched by the increased T2 signal visualized with MRI [13].

In most cases, a mutation of the tumor suppressor gene, NF2, takes place on chromosome 22. There are three types of NF2 distinguished according to their clinical presentation and severity: Wishart, Gardner and mosaic-type NF2. The Wishart variety appears in childhood or late adolescence and consists of bilateral vestibular schwannomas associated with medullary tumors, whereas the Gardner version appears later, is less debilitating, and presents as bilateral vestibular schwannomas with few meningiomas [13].

Malignant transformation is extremely rare for this type of tumor, although local recurrence following resection may be incomplete.

Clinical presentation and diagnosis

Thoracic schwannoma tumor growth is slow, resulting in a poor clinical condition with few or no symptoms, especially during the early stages. However, when the tumor reaches large proportions, frequently presenting as a bulky mediastinal mass, symptoms can arise as a consequence of the compression site, such as superior vena cava syndrome, dyspnoea or dysphagia [3,14].

Sometimes, schwannomas can develop in the trachea through the intercartilaginous membrane, forming an hourglass-shaped tumor. In the presence of bone erosion, severe pain or pathological fractures are common. In approximately 10% of cases, growth can exceed the intervertebral foramen and compromise the spinal canal by an hourglass-shaped growth that causes paraesthesia or paralysis. When this type of growth is evident, symptoms of intramedullary extension are found in 60% of cases [15,16].

Additionally, patients can present more severe signs, such as haemoptysis when the tracheobronchial tree is affected, or gastrointestinal bleeding, as in cases involving the oesophagus. Dysphonia can manifest with vagus nerve involvement prior to the origin of the recurrent nerve [17-19].

Schwannomas usually present alone, arising from any cranial or peripheral nerve, and it is very rare to find multiple schwannomas emerging from a single intercostal nerve [20].

The investigation of intrathoracic schwannomas begins with a full medical history and physical examination followed by imaging tests. The majority of lesions are diagnosed in young adults with no predominance of sex [3].

Chest radiography in posterior lateral incidence and profile is usually the first test to detect any changes. The visualization of the tumor becomes more acute when it reaches a large diameter, usually not common until symptoms arise resulting from occupation. Generally, this test defines which portion of the mediastinum is involved, but does not reveal tumor density or invasion of the medullary canal or adjacent structures [19].

Regarding computed tomography (CT) scanning, the tumor regularly presents itself as a homogeneous mass with soft tissue density [20-22]. The presence of hypodense areas correspond to areas of necrosis or haemorrhage. Neurilemmomas are characterized by several pathological areas: hypocellular areas adjacent to dense cellular areas or proximal to collagen or xanthomatous change [19,21].

Although less common, the mass can destroy the bone surrounding regions, resulting in CT images with

heterodensas areas. In CT, lesion appearance can be highly variable, but is usually well-circumscribed [22].

In contrast, magnetic resonance imaging (MRI) better defines the involvement of nerve plexi, vertebrae and the spinal canal. Hyperintense areas in T2 images correspond to cystic degeneration in the tumor. MRI must be performed in patients with suspicion of neurogenic tumors of the posterior mediastinum to exclude extension of the tumor in the intraspinal region [20]. As a result, from the moment the tumor develops, typical MRI signals (high intensity) can be observed that enable a very precise diagnosis. Thus, preoperative radiological assessment alone is sufficient, i.e., fine needle aspiration is unnecessary [23].

By defining tumor extension more precisely, MRI enables preoperative planning that is more sensitive than CT for delineating the presence or absence of invasion through the neural foramen and the degree of involvement of the vertebral canal [22]. The diagnosis can be confirmed intraoperatively and by histopathological analysis [21].

Ancient schwannomas are a rare variant of the tumor that presents degenerative histological changes that can lead to an incorrect diagnosis of malignancy. This rare status can simulate lung neoplasms on chest x-rays and CTs [24].

The radiological features of ancient schwannomas are not well-defined because of their rarity. However, the long-term progression of the tumor results in characteristic degenerative changes, such as cystic formation, calcification, haemorrhage and hyalinization. Its appearance on CT and MRI is typical of this type of tumor [19,21]. Solid components encapsulated with cystic areas, or the presence of cystic masses with marginal growth or with solid nodular components that present calcifications, are observed [25,26].

Certain authors suggest that a recommendation for surgical treatment must be considered when a patient has a hypervascular mass in soft tissues containing amorphous calcification on the simple scan and cystic areas on the MRI [21,22]. The suggestion is that calcification of soft tissue, which is visible in a simple scan, is a characteristic indicative of this pathological entity [27].

A definitive diagnosis is only possible after histopathological examination. The most significant histological characteristics of these tumors are the presence of a high degree of nuclear atypia as well as atypical hyperchromatic polymorphic cells and nuclei that frequently contain multiple lobes [24,28].

Fine needle biopsy can be useful in the diagnosis of anterior and posterior mediastinal tumors, but this technique is difficult to execute in the middle mediastinum because the amount of material is limited; thus, it is not recommended for diagnosing these processes [19,29].

Microscopy reveals two distinct types of tissue according to the Antonio classification: type A, corresponding to the cellular area, and type B, corresponding to the myxoid area. These two forms are usually associated in the same tumor.

Benign schwannomas are distinguished by the presence of a biphasic pattern (Antoni A and B) with the presence of Verocay bodies in the type A pattern. These bodies are formed by two parallel lines of nuclei with a space between them that is virtually anuclear [30].

Immunohistochemical analysis demonstrates immunoreactivity for the S-100 protein, just as reported for neurogenic tumors [31].

Thoracotomy x Thoracoscopy

The treatment of choice for mediastinal schwannomas is resection by videothoracoscopy or open thoracotomy [32]. Therefore, surgery is the main therapeutic route for neurogenic tumors of the mediastinum, and complete surgical resection is considered the gold standard [33].

The management of neurilemmomas located in the mediastinum is determined by the findings of CT or MRI exams. However, these only refer to intrathoracic tumors, or those that extend into the intervertebral channel based on visualization difficulties [22,34]. Benign neurogenic tumors rarely reappear, and simple enucleation is sufficient; no adjuvant therapy is required. The challenge is to preserve nerve function, particularly when the tumor occurs on the phrenic or vagus nerve [33].

Preservation of the recurrent laryngeal nerve is essential to prevent paralysis of the same, i.e., postoperative dysphonia. In resections of the vagus nerve below the origin of the recurrent nerve, no cardiac, bronchial

or gastrointestinal changes have been observed [35,36].

When the tumors originate on the intercostal nerves, if necessary, the nerve root can be sacrificed, resulting in relatively minor deficits [33].

It is important to note that episodes of bleeding, cerebrospinal fluid leakage through the intervertebral foramen and paraplegia may be consequences of complete resection attempts with mediastinal neurogenic tumors [37-39]. Assuming that the incomplete resection of the lesion does not affect a child's survival, surgeons are encouraged to try resection of these lesions by thoracoscopy [37-39].

However, video-assisted thoracoscopic surgery (VATS) is effective for the removal of mediastinal tumors in children, especially neurogenic tumors, as it enables complete resection, histological diagnosis of the lesion and absence of recurrence at the site of placement of the trocars [40].

In addition to the normal risks of thoracic surgery, such as haemorrhaging, infection and pulmonary morbidity, certain neurological complications can arise because of resection. Among these, those that should be mentioned include deficits like Horner's syndrome, partial sympathectomy, recurrent laryngeal nerve injury and paraplegia [33].

Thoracotomy is a viable approach for masses in the middle and posterior mediastinum and is also adequate for the anterior mediastinum if the mass is fully contained within one hemithorax and does not cross the midline [3].

VATS was fully adopted in the 1980s following technological improvements and consolidation of the laparoscopic technique. Indications for resection by VATS include biopsy to exclude malignancy, relief of compressive symptoms, preventing extension of a tumor into the spinal foramen and to thwart malignancy [6-8]. In VATS, the patient is positioned as per a lateral thoracotomy, and the camera is introduced into the fifth intercostal space, posteriorly for anterior mediastinal masses and anteriorly for posterior masses. Other accesses depend on the location of the mass. Postoperative recovery of neurological function depends on the type of surgery [3,7,14].

Among the majority of reported cases that exclusively employed the VATS technique to resect mediastinal masses, a high degree of success was obtained, demonstrating the safety of the procedure in the hands of properly trained surgeons. When compared with thoracotomy, VATS requires smaller incisions, reducing pain, causing fewer and less severe pulmonary complications, shortening hospitalization and promoting earlier return to activities and aesthetic gains. Prognosis after surgery is excellent, but local recurrence can occur following incomplete resection of the lesion [3].

In some cases, it is possible to complete resection of a mass while preserving important structures, especially if the mass is completely contained within a hemithorax.

If complete resection cannot be performed, a common situation when dealing with malignant tumors, postoperative radiation therapy is the recommended course of action. Occasionally, postoperative chemotherapy can also be efficacious [21,22].

The majority of mediastinal neurogenic tumors are present in the posterior compartment, and the best surgical approach is a standard thoracotomy. However, VATS is a superb option for simple neurogenic tumors [41,42].

Tumor excision is curative - the recurrence of benign schwannomas is unusual [19,43]. Malignant degeneration of a benign tumor has been described, though it is rare [44]. Although rare and infrequent, intrathoracic schwannomas of the vagus nerve should be included in the differential diagnosis of mediastinal tumors [19].

Conducting a preoperative assessment of intraspinal involvement is essential for diminishing the risk of haemorrhaging into the spinal canal and spinal cord damage [26-28]. When a tumor is identified in this region, the favored approach is thoracic surgery and neurosurgery. Initially, this process was performed in phases, beginning with a laminectomy and followed by a thoracotomy at a later date [16,45].

Currently, the preferred choice is performing the procedure in a single operation, where combined resection is the opted-for method. This can be conducted through separate incisions or a shared incision [4]. A single incision with a vertical component along the spine, and a curvilinear lateral extension, permits access to both specialties. Hence, a laminectomy can be

carried out to remove the intraspinal component, while the thoracic component can be excised by thoracotomy [10-12]. This allows for excision of the entire mass and minimizes the risk of undetectable haemorrhage inside the spinal canal, where a haemotoma could result in neurological deficit [16,45].

More recently, Vallieres et al. described an approach that uses posterior microneurosurgical techniques and an anterior VATS technique to perform a minimally invasive complete resection [46].

A careful preoperative assessment is essential for clarifying whether there is any spinal canal or neural foramen involvement so that the risks of hemorrhage and neurological damage can be significantly reduced [4-6]. Treatment involves complete surgical resection via thoracotomy or thoracoscopy with neurosurgical exploration to verify whether the tumor has extended into the spinal canal [23,24]. Although recurrence is rare and patients present a robust prognosis, as the tumor is benign, when dealing with malignant neurogenic neoplasms, prognosis is poor [3].

Fine needle biopsy can be performed; however, a precise diagnosis may not be possible because of limited cellularity. This raises the possibility of a misdiagnosis of malignancy because the appearance of histological degenerative changes may be seen. Surgical excision of the mass is the cornerstone of diagnosis and treatment of these potentially resectable tumors [47].

Conclusions

Intrathoracic schwannomas are often asymptomatic, and the lesion is usually detected in routine imaging tests. Thus, this diagnosis is a challenge and should not be discarded for a diagnostic hypothesis in the presence of mediastinal masses.

MRI is the preferred imaging technique for preoperative planning because it fosters clearer observation of the involvement of nervous plexi, vertebrae and the spinal canal.

The recommended treatment remains resection by thoracotomy or VATS, and recurrence of benign neurogenic tumors following these procedures is rare. Moreover, they do not require adjuvant therapy.

In addition to the risks common to any thoracic surgery, neurological complications should be taken into consideration when planning the surgical approach.

Among surgical approaches, open surgery continues to be the most common method for treatment. VATS assists in the realization of biopsies to exclude malignancy, to relieve compressive symptoms and to prevent extension of the tumor into the spinal foramen.

In cases where VATS is utilized for tumor resection, prognosis is favorable, but relapse can take place when the resection is incomplete, and complementary treatment with chemotherapy or radiotherapy is recommended.

In the literature, few cases of thoracoscopic mediastinal schwannomas exclusively treated by VATS have been reported. However, all surgical modalities are viable options, and the method should be applied on a case-by-case basis. In this context, the physician and patient should be similarly engaged in choosing the best method to achieve the expected result.

List Of Abbreviations

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

VATS : Video-Assisted Thoracoscopic Surgery

Authors' Contributions

All authors: 1) have made substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it critically for important intellectual content; and 3) have given final approval of the version to be published.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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