Appendicular schwannoma

Review of the literature on a rare benign tumor often mistaken for hyperplasia

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INTRODUCTION: *Appendicular schwannoma is a rare benign neoplastic proliferation of the appendicular Schwann cells. It is often asymptomatic until it occludes the appendicular lumen thus causing appendicitis-like symptoms.*
EVIDENCE ACQUISITION. *The neoplastic proliferation of the Schwann cells, although benign, may rarely degenerate into a malignant neoplasm, thus denoting the importance of diagnosis.*
Some Authors in the Literature used the term "neuroma" or "neurinoma" to indicate either a hyperplastic proliferation of the Schwann cells or its neoplastic but benign proliferation, thus raising the important question of a probable mistaking of these two different histologic entities.
The hyperplastic proliferation is usually subsequent to a chronic appendicular inflammation, and it is a more common finding in specimen of appendectomy.
EVIDENCE SYNTHESIS: *Aim of the study is to review the published scientific papers about the rare histologic entity of appendicular schwannoma and to define the not clear aspects of Schwann cell neoplasia versus hyperplasia. A review of the Literature from Medline/Pubmed has been accomplished. Forty-four studies from the Literature resulted suitable for our study.*
CONCLUSION. *Appendicular schwannoma has to be considered in patients with recurrent right lower quadrant pain, and may affect the patient's prognosis if it remains undiagnosed, since it may degenerate in malignancy. There is a lack of clarity in the Literature about the distinction between the hyperplastic and the neoplastic benign Schwann cells proliferation, which must be clarified. The meaning of the terms "neuroma" and "neurinoma" should be standardized, the first referring to the hyperplastic proliferation, and the second to the neoplastic but benign proliferation of the Schwann cells.*

KEY WORDS: Appendiciis, Appendectomy, Appendicular neuroma, Appendicular neurinoma, Appendicular schwannoma

Introduction

Stromal appendicular tumors are very rare and include neurogenic neoplasms, leiomyoma and gastrointestinal stromal tumors [1].
The appendicular schwannoma, also called "neurinoma", is a benign neoplastic proliferation of the Schwann cells. It is a rare often asymptomatic benign stromal tumor of neural origin mainly affecting young patients [2]. Few cases have been reported in the Literature so far [1-24].
Pre-operative diagnosis and differential diagnosis are difficult since their symptomatology is subsequent to underlying appendicitis. Radiologic findings are not specific [23] for both the histologic entities, and definitive diagnosis is made by the pathologists at the surgical specimen. Malignant degeneration is possible for the schwannoma [1], and although it is rare, it may affect the patient's prognosis.
Likely for similarity of terms, some Authors in the Literature indiscriminately used the term "neuroma" or "neurinoma" to indicate either a hyperplastic proliferation of the Schwann cells or its neoplastic but benign proliferation, thus raising the important question of a

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probable interchange of these two different histologic entities. The similarity of terms often leads to confusion among non-pathologists, so that these two histologic figures may be interchanged.
Differently from the appendicular schwannoma or neurinoma, the appendicular neuroma is a hyperplastic proliferation of the Schwann cells and nervous fibers often subsequent to a chronic inflammation. It is a frequent incidental histologic finding after appendectomy for acute appendicitis.
Aim of the study is to review the published scientific papers about the rare histologic entity of appendicular schwannoma and to define the not clear aspects of Schwann cell neoplasia and hyperplasia.

Evidence Acquisition

A review of the Literature from Medline/Pubmed has been accomplished. The string "appendicular schwannoma" gave 20 results, the string "appendicular neurinoma" gave 14 results and the string "appendicular neuroma" gave 49 results. Only pertinent papers whose full text or abstract was available were selected. Repeated papers were considered once. Specific collected data were (where available): number of cases, age, sex, symptoms, associated colonic pathologies, radiologic findings, tumor dimension and localization inside the appendix, surgical procedure. The record available was reported in Table I.
A total of 83 studies from the Literature were found. Forty-four papers resulted suitable for our study. Few of them reported more complete information. No significant difference in age, gender, or body mass index was found. One case was associated to colonic diverticula and another one to neurofibromatosis. The main symptoms were lower right abdominal pain with fever, and urinary symptoms that presented when a complication occurred. The main appendicular localization was the apex. Either symptoms or radiologic findings were aspecific.
Appendicular schwannoma or neurinoma is a rare benign tumor, which can mimic symptoms of acute appendicitis. It is described in the Literature indistinctly either as a neurogenic appendicopathy [22] or a rare neurogenic benign neoplasm [1,23] of unknown pathogenesis [22].
Few cases have been reported in the Literature about appendicular neurinoma [1-24]. Although it is a rare tumor, the wide range of incidence (about 0,004-7,5% of all the histopathologic appendicular findings from appendectomy and from autopsies) [2,3,25-27] can be a bias. Appendicular localization of neurinoma is rare also in neurofibromatosis patients with gastrointestinal involvement [23].
Sesia et al. [2] examined appendix specimens from 385 children, 29 (7.5%) of them were appendicular neuroma at the histopathological exam. All the patients presented with recurrent right lower quadrant pain or signs of acute appendicitis.
Yilmaz [28] retrospectively reviewed the medical records of 338 liver living donors. One hundred twenty six of them underwent incidental appendectomies. Histopathologic examination of appendix specimens revealed 1 appendicular neuroma (0,8%) and 1 carcinoid tumor (0,8%).
Dincel et al. [22] reviewed the files of 1970 patients subdue to appendectomy for acute appendicitis. Rare his-

Table I - *Data available from the Literature on appendicular schwannoma.*

Authors	N	%	Sex	Age (years)	Symptoms	Associated pathologies	Dimension	Localization	Radiology	Surgery
Lund [24]	1		F	54	Urinary infection, pneumaturia	Colonic diverticula	-	Apex	Fistula between appendix and bladder	Open
Esterson [23]	1		F	30	Urinary symptoms	Neurofibromatosis type 2	6 cm	Apex	CT+MRI: well-circumscribed mass with homogeneous enhancement	Laparoscopy
Molina [1]	1		M	32	Fever, pain	-	-	-	CT: inflammation around the appendix	Open
Sesia [2]	29/385	7,5%		Children	Acute appendicitis like	-				
Yilmaz [28]	1/126	0,8%		Adults	None	None (liver donors)	-	-	-	Open
Dincel [22]	3/59	0,15%			Acute appendicitis					
Schmutzer [3]	5/8699	0,49%								
Stanley [11]	20									

tologic features were found in 59 patients, 3 of these were appendicular neuroma (0,15%).
Schmutzer et al. [3] performed 8699 appendectomies and found 43 carcinoids (0,49%) and 5 neuromas (0,05%).
There is no unanimity in the Literature about the age of onset. Sesia et al. affirmed that hyperplastic appendicular neuroma is a relatively common finding in children [2], but Pina-Oviedo et al. described it as a relatively common entity in adults and rare in children [8]. Probably, it arises in young age and is discovered during the adult age.
The appendicular neurinoma shows positivity for S-100 protein in the Schwann cells, and neuron-specific enolase [8,11,12,29,30], distributed in a diffuse pattern of lymphoid and adipose tissue. The secretion of neuropeptides by the extra-epithelial enteroendocrine cells-such as serotonin, substance P and bradykinins-may be the possible etiology for the associated pain, mimicking acute appendicitis [31-33].
Stanley et al. [11] reported 20 cases of appendicular neuromas that were analyzed at light-microscopic, immunehistochemical and electron-microscopic. By light-microscopy, appendicular neuromas appeared as proliferation of spindle cells in a myxoid background, with connective tissue and eosinophils. Seventeen were located centrally in the appendix without nodule formation. One was a central nodule and two were confined to the mucosa. The spindle cells were positive for S-100 protein and neuron-specific enolase in all cases. In 12 cases, serotonin positive cells entrapped in the proliferation were present. Two appendicular neuromas contained somatostatin positive cells. Ultrastructural examination did not confirmed the presence of vasoactive intestinal polypeptide, substance P, neurotensin, bombesin and gastrin, and one case presented neurosecretory granules.
Appendicular schwannoma gives rise to symptoms mimicking acute appendicitis [1,2]. The neoplastic proliferation of Schwann cells, neuroendocrine cells with neurosecretory granules [11,34] and non-myelinated nerve cells [1,8] occludes the appendicular lumen causing fibrosis in 5-65% of cases [8,11,12,22] and an inflammatory state [1,11,22,29,35], with consequent non-specific symptomatology often misunderstood with acute appendicitis or acute abdomen [1,2].
Molina et al. [1] reported a case of a 32 years old male with recent onset of fever and pain at the upper abdomen, then migrated to the lower right quadrant. Blood exams revealed leukocytosis with neutrophilia and an elevated C reactive protein. CT scan revealed inflammation around the appendix. Appendectomy was performed. Pathologic exam revealed obstruction of the appendicular lumen by a proliferation of neural fusiform cells, having immunoreactivity to S-100 protein and Neuron-specific enolase without atypia. Neuroma of the appendix was the final diagnosis.
The diagnosis remains histopathological [23]. The differential diagnosis should be made considering other appendicular neoplasms such as carcinoid tumor, adenoma, adenocarcinoma, mucinous adenocarcinoma and lymphoma [36].
Some Authors attributed the neural proliferation in appendectomy specimens to long-term sub-acute appendicitis, chronic appendicitis, and intermittent obstruction [37,38], but did not distinguish between hyperplasia or benign neoplastic proliferation of the neural cells. Probably the neural proliferation due to long-lasting inflammation is a hyperplasia, and it can be confirmed by the high frequency of that histologic finding in inflamed appendix.
The radiologic findings are aspecific. At CT scan and MRI, appendicular schwannoma may appear as an appendicular enlargement with wall thickening and no periappendicular fat edema. At enhanced-contrast CT and MRI, it appears as a homogeneous enhancement with a central elongated fluid signal [23].
The appendicular schwannoma tends to involve the surrounding organs with a behavior of invasiveness although benign.
Lund et al. [24] reported a case of benign appendicular neuroma in a 54-year-old woman presenting with recurrent urinary tract infections and pneumaturia. Cystoscopy showed a small diverticulum with no sign of fistula. Since the patient was affected by colonic diverticula, a fistula between the colon and the bladder was suspected. At laparotomy, a fistula between the apex of the appendix and the bladder was discovered. Appendectomy with excision of the fistula and closure of the bladder wall were performed. The appendix did not show signs of inflammation or malignancy.
Esterson et al. [23] reported a case of a 30 years old woman affected by neurofibromatosis type 2 who complained urinary symptoms. The ultrasonografic exam and the contrast-enhanced CT scan revealed a well-circumscribed right pelvic mass measuring 6 cm at the appendicular apex. The mass was separated by the right ovary. The contrast-enhanced MRI scan, the mass had hypointense T1 signal, intermediate T2 signal, and homogeneous enhancement and a thin elongated fluid signal centrally along the mass. A diagnostic laparoscopy was performed. The appendix was visualized with a large mass at its tip without evidence for local invasion. Appendectomy was performed and the mass identified as ganglioneuroma was totally excised.
The curative treatment is surgical excision [1]. When a patient presents signs and symptoms of acute appendicitis, the possibility to find an appendicular schwannoma should be considered. In any case, if a schwannoma is suspected, appendectomy must be performed also if asymptomatic, because of the possible malignant degeneration [1].
The appendicular schwannoma may degenerate into malignant tumor [8,11,22,29,31,35] in 5-15% of cases [39], as a precursor of carcinoid [8,31]. The appendicular carcinoid may manifest with signs and symptoms of acute appen-

dicitis 22. Appendectomy is the adequate treatment if the dimension of carcinoid is inferior to 1 cm, since the risk of metastasis is very low [22]. If a malignant neoplasm of the appendicitis is found and is bigger than 2 cm, the surgeon must be aware of the possibility to perform right hemicolectomy, since the risk of metastasis is up to 85% [40-43].

Evidence Synthesis

Asymptomatic appendicular schwannoma is a rare but threatful histologic entity which may affect the patient's prognosis [1] if it remains undiagnosed, since it may silently degenerate in malignancy becoming potentially life threatening. For this reason, appendectomy should be performed when symptoms of acute appendicitis are relapsing or difficult to treat. Furthermore, every appendectomy must be followed by the histopathological examination, in order to discover any potential malignant lesion.

Review of the Literature arose a problematic question. There is another histologic feature also called appendicular neuroma, wrongly considered as a tumor. Actually, neuroma is a focal hyperplastic proliferation of Schwann cells and nerve fibers encribed to the traumatic neuroma [30] or amputation neuroma or stump neuroma, secondary to a peripheral nerve damage that occurs after its complete interruption for a focal trauma, acute or chronic inflammation, or surgery. Typically, the neuroma is found in the limbs after amputation or partial transection [44], but the appendix is a possible localization. It represents the outcome of an ineffective attempt at regeneration of the nerve itself. Appendicular neuroma is often asymptomatic and is incidentally found after appendicectomy for long-lasting acute appendicitis at the specimen.

The above-mentioned Literature indiscrimately cited "neurinoma" and "neurinoma" as synonyms of a unique histopathological entity: the schwannoma.

Stanley and Aubock [11,34] referred the appendiceal neural proliferation to neuroma, neurogenous hyperplasia, neurogenic appendicitis, neuromatosis, traumatic neuroma, fibrous obliteration, axial neuroma, neurogenic appendicopathy, neuroimmune appendicitis, and appendiceal fibrosis. They described the appendicular neuroma as a rare benign tumor, but as a contradiction they reported that it is characterized by hyperplasia without atypia.

Molina et al. [1] described as neuroma a proliferation of neural fusiform cells obstructing of the appendicular lumen, having immunoreactivity to S-100 protein and Neuron-specific enolase without atypia. Although the lesion did not have atypia, the Authors recommended a close follow-up, thus raising doubts on the hyperplastic nature of the lesion.

The relative high frequency of appendicular neuroma reported by Sesia et al. [2], the wide range of incidence and the absence of unanimity in the Literature about the age of onset, rise the doubt of having considered either neuroma or neurinoma as the same histopathological finding.

Conclusions

In conclusion, appendicular schwannoma should be considered in patients with recurrent right lower quadrant pain, and may affect the patient's prognosis if it remains undiagnosed, since it may degenerate in malignancy. The Literature lacks of clarity between two similar but deeply different histologic entities, Schwann cells hyperplasia and Schwann cells neoplasm, and the confusion is fueled by the use of the two similar terms "neuroma" and "neurinoma". The meaning of these terms should be standardized, the first referring to the hyperplastic proliferation, and the second to the neoplastic but benign proliferation of the Schwann cells.

Riassunto

Lo schwannoma appendicolare è una rara proliferazione neoplastica benigna delle cellule di Schwann della parete della struttura. È spesso asintomatico fino a quando non occlude il lume della struttura causando sintomi simili all'appendicite acuta.

La proliferazione neoplastica delle cellule di Schwann, sebbene benigna, può raramente degenerare in una neoplasia maligna, motivando pertanto l'importanza della diagnosi puntuale.

Alcuni Autori in Letteratura hanno utilizzato il termine "neuroma" o "neurinoma" per indicare rispettivamente una proliferazione iperplastica delle cellule di Schwann o una sua proliferazione neoplastica ma benigna, sollevando così l'importante questione di un probabile equivoco tra queste due diverse entità istologiche.

La proliferazione iperplastica è solitamente successiva a un'infiammazione appendicolare cronica ed è un reperto più comune nei campioni di appendicectomia.

Scopo dello studio è rivedere i lavori scientifici pubblicati sulla rara entità istologica dello schwannoma appendicolare e definire gli aspetti non chiari della neoplasia a cellule di Schwann rispetto all'iperplasia. È stata effettuata una revisione della letteratura da Medline/Pubmed. Quarantaquattro studi della Letteratura sono risultati idonei per il nostro studio.

Lo schwannoma appendicolare deve essere preso in considerazione nei pazienti con dolore ricorrente al quadrante inferiore destro e può influenzare la prognosi del paziente se rimane non diagnosticato, poiché può degenerare in tumore maligno. C'è una mancanza di chiarezza in Letteratura sulla distinzione tra proliferazione iperplastica e neoplastica benigna delle cellule di

Schwann, che deve essere chiarita. Andrebbe standardizzato il significato dei termini "neuroma" e "neurinoma", il primo riferito alla proliferazione iperplastica, ed il secondo alla proliferazione neoplastica ma benigna delle cellule di Schwann.

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