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Clinicopathologic characteristics and surgical management of schwannomas of the upper digestive tract

AIM: *Schwannoma is a peripheral nervous system tumor arising from Schwann cells of the neural sheath, and they are very rarely seen in the upper digestive tract. In this study, we aimed to present the clinicopathologic characteristics and surgical management of patients who underwent surgical treatment for esophageal or gastric schwannoma.*
MATERIAL AND METHODS: *Patients who were diagnosed with esophageal or gastric schwannoma between January 2013 and January 2020 were included in the study. Demographic, clinicopathological and immunohistochemical parameters of the patients were analyzed along with the follow-up results.*
RESULTS: *There were 13 patients in our study. Nine patients had gastric schwannoma and 4 patients had esophageal schwannoma. Female gender was dominant (61.5%). The mean age was 56 years. Esophageal tumors were all enucleated. Minimal invasive approach was preferred in 3 patients. Gastric tumors were most commonly localized in the lesser curvature. Three patients underwent laparoscopic wedge resection, 3 patients open wedge resection, 2 patients subtotal gastrectomy, and one patient proximal gastrectomy. Intraoperative or postoperative complications did not develop in any patient. No patient required reoperation, and there were no deaths within 90 days postoperatively. In the postoperative 90-day period, there was no unplanned re-admission to the hospital. The mean follow-up period was 53.4 months (range: 23-93 months). No recurrence was detected in any patients.*
CONCLUSIONS: *Definitive diagnosis of schwannomas is made only by histopathologic examination postoperatively. S-100 expression has diagnostic significance. The preferred treatment is complete surgical excision with negative margins, and the long-term outcome is excellent as these lesions are mostly benign.*

KEY WORDS: Esophagus, Enucleation, Schwannoma, Stomach, Wedge resection

Introduction

Schwannoma is known as a rare tumor of the peripheral nervous system originating from Schwann cells. Generally, the term "*schwannoma*" refers to a benign, slow-growing tumor [1-3].

Gastrointestinal schwannomas (GSs) are rare and most originate in the stomach or bowels. They represent 2-7% of mesenchymal gastrointestinal tumors and account for 0.2% of all gastric tumors [4]. Esophageal schwannomas are sporadic and are the least common esophageal submucosal tumors. They constitute approximately 2% of all esophageal tumors [5]. GSs are usually asymptomatic. A small number of symptomatic cases show nonspecific symptoms such as abdominal pain, palpable mass, changes in bowel habits and gastrointestinal bleeding. Endoscopic examination, endoscopic ultrasonography (EUS) and computed tomography (CT) can be used for diagnosis. However, the specificity of these methods is low. Definitive diagnosis is made only by postopera-

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tive histopathologic examination and immunohistochemical methods [1,6]. The diagnosis of schwannoma is based on positive immunohistochemical staining for S-100 protein and negative results for CD34, CD117, desmin, and smooth muscle actin (SMA) [2,3].
Data on GSs in the literature consist of case reports and case series. Although there is a limited number of large-scale series, there are differences in the management of this tumor [1,5,7,8]. Though GSs are usually benign tumors and grow slowly, the recommended treatment is surgical excision. Endoscopic resection, laparoscopic or open surgery are all applicable methods. The choice of treatment varies depending on the tumor size and location and the surgeon's experience. Minimally invasive approaches have been shown to be superior in GSs as in other tumors [9,10].
Discussions in the literature regarding the clinical features, perioperative management, histopathological features and prognosis of GSs have been continuing [1,9,11]. In this study, we aimed to present the clinicopathologic features and surgical management of patients who underwent surgical treatment for esophageal or gastric schwannoma in the light of the literature.

Material and Methods

Patients who were diagnosed with esophageal or gastric schwannoma according to histological and immunohistochemical features between January 2013 and January 2020 were included in the study. Clinical information was obtained from the medical records of patients.
Demographic data, body mass index (BMI), American Society of Anesthesiologists (ASA) score, admission symptoms, tumor localization, histopathological and immunohistochemical properties of tumors, surgical procedures, intraoperative complications, postoperative complications, postoperative hospital stay, unplanned reoperation, postoperative 90-day mortality, 90-day unplanned re-admission to the hospital, mean follow-up time and current clinical status were analyzed.

Table I - *Demographic data and symptoms of patients with gastrointestinal schwannoma*

Characteristic Gender	Value n (%)
Male	5 (38.5%)
Female	8 (61.5%)
Age (years)	56.3±6.9 (range; 45-67)
BMI (kg/m^2)	23.7±1.8 (range; 21.3-27.4)
ASA score	
1	7 (53.8%)
2	6 (46.2%)
Symptoms	
Abdominal pain	9 (69.2%)
Dysphagia	4 (30.8%)

All tumors were examined histopathologically with preparations stained with hematoxylin and eosin. Immunohistochemical markers studied were S-100, CD34, CD117, DOG-1, desmin, vimentin, smooth muscle actin (SMA), epithelial membrane antigen (EMA), neurofilament protein (NFP), neuron specific enolase (NSE) and glial fibrillary acidic protein (GFAP). Ki-67 index and mitosis numbers [50 high-power fields (HPFs)] were calculated.
Before the operation, endoscopic examination, EUS and thoraco-abdominal CT were performed in all patients. The treatment method was decided according to the location and size of the lesion.

Statistical Analysis

IBM SPSS Statistics for Windows, version 24 (IBM Corp, Armonk, NY, USA) package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean and standard deviation (median and minimum-maximum where necessary).

Results

There were 13 patients in our study. Nine patients had gastric scwannoma and 4 patients had esophageal scwannoma. Female gender was dominant (61.5%). The mean age was 56 years. The mean body mass index (BMI) was 23.7 kg/m^2. Seven patients had ASA 1 score and 6 patients ASA 2 score. Abdominal pain was the most common presenting symptom. The demographic and

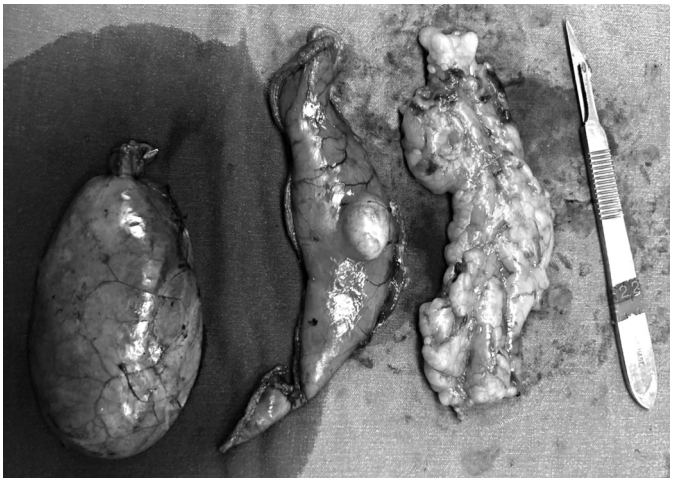

Fig. 1: Cholecystectomy material, gastric resection material and omental resection material are seen in the picture from left to right. In the gastric resection material, a dirty gray, brown mass lesion with a size of 5.5x4x4 cm exceeding serosal layer was observed at a distance of 1.2 cm from the close surgical border.

TABLE II - *Clinicopathologic characteristics and follow-up data of patients*

Case Number	Age/Sex	Tumor location	Operation	Postoperative hospital stay (days)	Follow up (months)
1	55/M	Gastric corpus-antrum junction	Laparoscopic gastric wedge resection	3	66, NED
2	61/F	Esophagus	Enucleation (VATS)	4	51, NED
3	50/F	Gastric body(lesser curvature)	Proximal gastrectomy	9	77, NED
4	63/F	Esophagus	Enucleation	11	93, NED
5	52/F	Esophagus	Enucleation (VATS)	6	45, NED
6	63/M	Gastric body(lesser curvature)	Gastric wedge resection	7	30, NED
7	57/M	Gastric body(lesser curvature)	Subtotal gastrectomy	8	27, NED
8	64/F	Esophagus	Enucleation (VATS)	5	59, NED
9	45/F	Gastric corpus-antrum junction	Laparoscopic gastric wedge resection	5	62, NED
10	56/F	Gastric corpus-antrum junction	Laparoscopic gastric wedge resection	8	44, NED
11	67/M	Gastric body(lesser curvature)	Gastric wedge resection	10	73, NED
12	54/M	Gastric body	Gastric wedge resection	4	45, NED
13	46/F	Gastric antrum	Distal subtotal gastrectomy	6	23, NED

M: Male, F: Female, VATS: Video-Assisted Thoracic Surgery, NED: No Evidence of Disease

clinical characteristics of patients are shown in (Table I). Enucleation was performed in all esophageal tumors. Minimally invasive approach was preferred in 3 patients. Gastric tumors were localized mostly in the lesser curvature. Three patients underwent laparoscopic wedge resection, three patients open wedge resection, two patients subtotal gastrectomy, and one patient proximal gastrectomy. The mean hospital stay was 6.6 days (range: 3-11 days). Intraoperative or postoperative complications did not develop in any patient. No patient required reoperation, and there were no deaths within 90 days postoperatively. In the postoperative 90-day period, there was no unplanned re-admission to the hospital. The mean follow-up period was 53.4 months (range: 23-93 months). No recurrence was detected in any patients. Clinicopathologic characteristics and follow-up data of patients are presented in (Table II).

Macroscopically, in the gastric resection material, a dirty gray, brown colored mass lesion was observed (Fig. 1). Microscopically, neoplastic development with compact hypercellular Antoni A areas and myxoid hypocellular Antoni B areas were observed in histological sections (Fig. 2). Nuclear palisading around fibrillary process (Verocay bodies) was often seen in cellular areas (Fig. 3). Focal lymphoid aggregates were traced around the stroma and around the tumor.

No necrosis, pleomorphism and mitotic activity were observed in the tumor. S-100 stained positive with immunohistochemical method (Fig. 4). CD34,CD117, Desmin, SMA, CD56, and HMB45 were all negatively stained. The findings were consistent with a schwannoma. The mean tumor diameter in patients was 39 mm and the largest tumor diameter was 70 mm. The surgical margin was negative in all patients. The Ki-67 index was 3-4% in one patient and 1-2% in other patients. S-100 was positive in all patients. Histopathologic and immunohistochemical characteristics are given in (Table III).

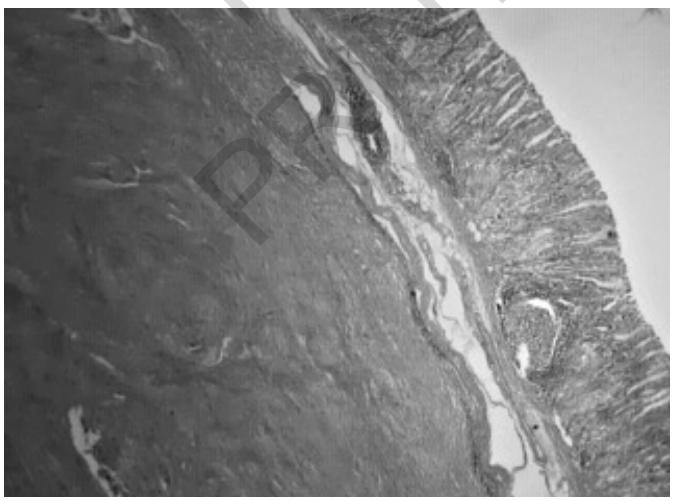

Fig. 2: Schwannoma covered with gastric mucosa (HE, x 100).

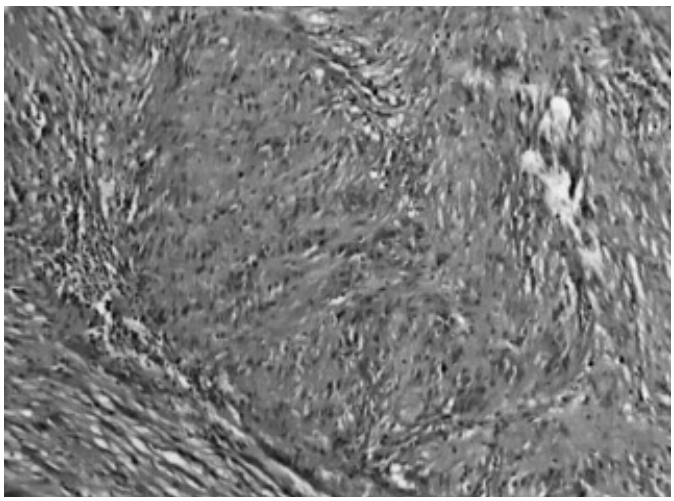

Fig. 3: Verocay bodieis in cellular areas (HE, x 200).

Table III - Histopathologic and immunohistochemical characteristics of patients

Case	Tumor size (mm)	Mitoses (50 HPFs)	Margin Status	Ki-67	Immunohistochemistry
1	35	1	negative	1-2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-)
2	15	0	negative	1-2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-)
3	70	0	negative	1-2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-), EMA (-), NFP (-)
4	60	0	negative	2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-)
5	30	0	negative	1-2%	S100 (+), SMA (-), Desmin (-), Vimentin (-), CD34 (-), CD117 (-), Dog1 (-)
6	45	0	negative	1-2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-), EMA (-)
7	60	0	negative	1-2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-), EMA (-), NFP (-)
8	20	0	negative	1-2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-)
9	25	0	negative	1%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-)
10	30	1	negative	1%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-)
11	50	0	negative	1%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-)
12	15	2	negative	3-4%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (+), Dog1 (-), GFAP (+)
13	55	0	negative	1-2%	S100 (+), SMA (-), Desmin (-), CD34 (-), CD117 (-), Dog1 (-), CD56 (-)

HPFs: High-Power Fields, SMA: Smooth Muscle Actin, EMA: Epithelial Membrane Antigen, NSE: Neuron Specific Enolase, NFP: Neurofilament Protein, GFAP: Glial Fibrillary Acidic Protein

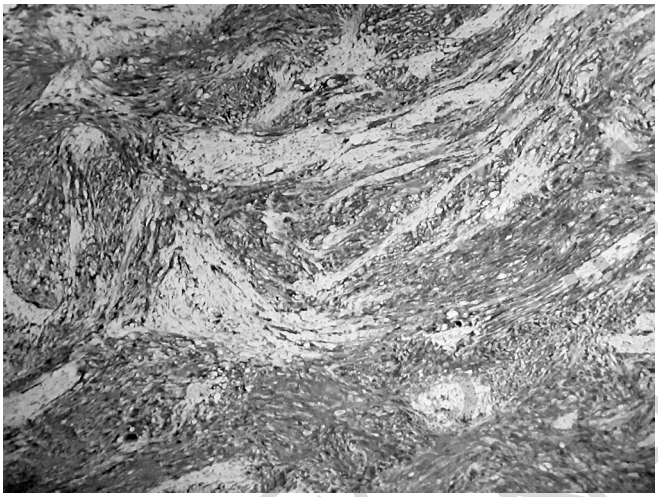

Fig. 4: S-100 positivity in tumor cells (S-100, x 200).

Discussion

Esophageal schwannoma was first described by Chatelin and Fissore in 1967 [12], while gastric schwannoma was first described by Daimaru *et al,* in 1988 [13]. Schwannomas of gastrointestinal tract originating from the Auerbach nerve plexus located in the muscularis propria layer in the wall of the gastrointestinal system are extremely rarely seen tumors [4,9].

In the large series published in the literature, esophageal schwannomas develop more frequently in middle-aged women, and are often found in the proximal esophagus [8,12]. Schwannomas originating from the stomach are usually seen in the fifth and sixth decade of life, and they occur 2 times more frequently in women than in men. The most common location is body of stomach, followed by fundus and antrum [6,9]. In our series, in accordance with the literature, upper gastrointestinal tract schwannomas were more common in women in the 6th decade, and in terms of localization, they were more frequently seen in the proximal part of the esophagus and in the corpus of the stomach.

Although patients are generally asymptomatic, they can also present with complaints such as dysphagia, abdominal pain, gastrointestinal bleeding, and long-term weight loss due to luminal narrowing in the tumors of esophagus [6,14]. In our series, patients with gastric localization generally presented with nonspecific abdominal pain, and they were operated on according to the endoscopic examination result. In the esophageal localization, the major symptom was dysphagia. BMI of these patients were lower when comparing with the patients with gastric schwannoma.

Diagnosis of GSs is usually delayed due to subclinical growth of the tumor. Since GSs generally originate from the muscularis propria in the submucosa, they are covered with intact mucosa and endoscopic biopsy is not suitable for diagnosis [3,5]. Tumors that stand out in the main differential diagnosis of GSs are gastrointestinal stromal tumors (GISTs). Although the clinical, histological and demographic features of these two tumors are similar, their treatment and prognosis are very different [2,10,15]. Immunohistochemical markers guide us in the differential diagnosis of mesenchymal tumors. Desmin and SMA positivity indicate smooth muscle originated lesions such as leiomyoma or leiomyosarcoma. CD34 and CD117 positivities indicate GISTs. S-100 strong positive staining supports the diagnosis of GSs [1,3,16,17]. In our series, S-100 immunohistochemical marker was positive in all patients in accordance with the literature. We found the mean tumor diameter to be 3.9 cm and all surgical margins were negative. Ki-67 index was 3-4% in one patient and 1-2% in other patients. In our series, the mitotic index of tumors were very low (range: 0-2).

Surgical treatment is curative in most of the cases with gastric schwannoma. Wedge resection, subtotal or total gastrectomy without lymph node dissection are sufficient to achieve negative surgical margins. As in other soft tissue sarcomas, schwannomas rarely metastasizes to lymph nodes, and therefore surgical lymphadenectomy is not routinely performed. The location and diameter of tumor are important in the selection of treatment method [10,16]. As in other gastric tumors, the superiority of laparoscopic approaches in the postoperative period has also been shown in GSs [2]. Although all patients were not operated with minimally invasive technique, re-admission to the hospital, reoperation and 90-day mortality, which are indicators of postoperative quality, were not observed in any patient in our series. Moreover, there were patients who were operated on by open surgery which prolonged the length of hospital stay in our series.

The therapeutic management of esophageal schwannoma depends on various factors such as the patient's clinical complaints, tumor size and complications due to tumor growth. Chemotherapy and radiation therapy are ineffective. Surgical treatment modalities include enucleation and esophagectomy. The most commonly preferred treatment is enucleation surgically or endoscopically. The surgical method can also be applied minimal invasively. Enucleation is recommended for smaller tumors, while esophagectomy is recommended for larger tumors [5,18]. In our series, tumor size was effective in determining the surgical method. While thoracotomy was performed for larger tumors, minimally invasive procedures were applied to other small tumors.

Schwannomas have a good prognosis and generally do not recur or metastazise. Relapse has often been associated with an incomplete surgical margin in malignant cases. Therefore, it should be kept in mind that the malignant potential of schwannoma should be determined before surgery. In fact, it is difficult to differentiate malignant lesions from benign ones with preoperative imaging methods. For this reason, negative surgical margins should be reached and care should be taken not to rupture the tumor intraoperatively. In schwannomas, a diagnosis of malignancy is made with the presence of mitotic figures, nuclear atypia, necrosis and other pathological features [4,9,16]. The recommended oncologic follow-up time for benign gastric schwannoma is controversial. For this tumour, which has a low probability of recurrence, no recurrence has been detected in the median follow-up periods ranging from 22-132 months in the literature [11]. In our series, the mean follow-up time was 53.4 months, and the follow-up time ranged in the interval of 23 to 93 months, and no recurrence was detected during this follow-up period. We attribute this to the low Ki-67 index and the mitotic rate, and the absence of malignant patients in our series. In addition, negative surgical margins undoubtedly contribute greatly to the occurrence of this situation.

The main limitations of our study were that the study was retrospective in design and the tumours were not analyzed for genetic mutations by next generation sequencing.

Conclusion

Schwannomas are a clinical entity that should be considered in the differential diagnosis of gastrointestinal mesenchymal tumors. The prognosis of these tumors with low malignancy potential is good. Surgical resection with negative surgical margins is the recommended treatment method. Resections can be done safely with minimally invasive approaches. However, it is clear that molecular genetic and oncologic studies are needed to better understand the characteristics of schwannomas.

Riassunto

SCOPO DELLO STUDIO: Lo Schwannoma è un tumore del sistema nervoso periferico derivante dalle cellule di Schwann della guaina neurale e si incontrano molto raramente nel tratto digerente superiore. Lo scopo di questo studio è quello di considerare le caratteristiche clinicopatologiche e la gestione chirurgica dei pazienti sottoposti a trattamento chirurgico per schwannoma esofageo o gastrico.

MATERIALI E METODI: Sono stati inclusi nello studio i pazienti a cui è stato diagnosticato uno schwannoma esofageo o gastrico tra gennaio 2013 e gennaio 2020, analizzando gli elementi demografici, clinicopatologici e immunoistochimici oltre ai risultati del follow-up.

RISULTATI: Sono entrati nello studio 13 pazienti, nove con schwannoma gastrico e 4 con schwannoma esofageo. Il sesso femminile era dominante (61,5%). L'età media era di 56 anni. I tumori esofagei sono stati tutti enucleati con approccio mininvasivo preferito in 3 pazienti. I tumori gastrici erano più comunemente localizzati nella picccola curvatura: tre pazienti sono stati sottoposti a resezione laparoscopica a cuneo, 3 pazienti a resezione a cuneo in laparotomia, 2 pazienti sono stati trattati con gastrectomia subtotale e un paziente con gastrectomia prossimale. Non si sono registrate complicanze intraoperatorie o postoperatorie in nessuno dei pazienti. Per nessun paziente c'è stata necessità di un reinterbento e non si sono verificati decessi entro 90 giorni dall'intervento. Nel periodo postoperatorio di 90 giorni, non vi è stato nessun nuovo ricovero ospedaliero programmato. Il periodo medio di follow-up è stato di 53,4 mesi (range: 23-93 mesi). Non è stata registrata alcuna recidiva in nessuno dei pazienti.

CONCLUSIONI: La diagnosi definitiva degli schwannomi viene fatta solo dall'esame istopatologico postoperatorio. L'espressione di S-100 ha un significato diagnostico. Il trattamento preferito è l'escissione chirurgica completa con margini negativi e il risultato a lungo termine è eccellente poiché queste lesioni sono per lo più benigne.

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