Malignant peripheral nerve sheath tumour of the oesophagus

Review of the literature and report of a case with lymph node and distant metastases

Ann. Ital. Chir., 2016 87: 26-38
pii: S0003469X1702509X

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Malignant Peripheral Nerve Sheath Tumour of the Oesophagus. Review of the literature and report of a case with lymph node and distant metastases

Oesophageal sarcomas are very rare while various histological types have occasionally been reported. Malignant Peripheral Nerve Sheath Tumour (MPNST) of the oesophagus is an exceedingly rare type of oesophageal sarcoma with only thirteen cases previously reported in the world literature. However, it should be included in the differential diagnosis of oesophageal neoplasias. Due to the small number of reported cases, the information about the biological behaviour of this entity is still insufficient. While MPNST is generally considered an aggressive type of tumour with high recurrence rates after surgical treatment and poor prognosis, previous reports of cases with oesophageal localization have recorded satisfactory outcomes overall even with less aggressive therapeutic approaches, although a long-term follow-up is lacking. Herein, we present the case of a 76-year-old female patient with oesophageal MPNST who presented with lymph node and distant metastases at the time of diagnosis, accounting for the second time only that this unusual presentation of this extremely uncommon disease has been reported. In our case, the course of disease was extremely aggressive which resulted in the second recorded death from this entity in the literature. The case presentation is followed by an extensive review of the world literature for the so far reported cases, aiming to highlight all relevant aspects such as demographics, clinical features, diagnostic assessment and findings, histological parameters, treatment and prognosis, and extract valuable previously unpublished conclusions for this rare entity.

KEY WORDS: Lymph node metastasis, Malignant Peripheral Nerve Sheath Tumour, Malignant schwannoma, Neurogenic sarcoma, Oesophagus, S100.

Introduction

Mesenchymal tumours of the oesophagus are rare while most represent leiomyomas, lipomas and gastrointestinal stromal tumours (GIST) [1-4]. The most common primary neoplasms of the mediastinum are neurogenic tumours and schwannomas are the most common amongst them, accounting for 8% of all cases [3-5]. However, these tumours are rare in the gastrointestinal tract (GI) [2,6] and oesophageal localization is extremely rare [1-4,7].

Even rarer, are the oesophageal sarcomas including carcinosarcoma, which account for 0.1-1.5% of all oesophageal neoplasias [6,8]. Approximately 400 cases of oesophageal sarcoma have been reported so far. Pure sarcomas are exceedingly rare [6,8] and leiomyosarcoma is the most common type [8]. Sarcomas with mixed epithelial and spindle cell histological characteristics such as carcinosarcoma occur more frequently [8].

Pervenuto in Redazione Dicembre 2015. Accettato per la pubblicazione Marzo 2016.
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Only 13 cases of Malignant Peripheral Nerve Sheath Tumour (MPNST) of the oesophagus have previously been reported in the literature accompanied by immunohistochemical data for confirmation of the diagnosis [1-7,9-14]. Our case is the fourteenth without including cases of mixed-type tumours which represent different histological types with different biological behaviour. MPNST is an unusual type of soft tissue sarcoma of ectomesenchymal origin [15,16]. The term "MPNST" was introduced by the World Health Organization (WHO) in 2002 in order to unify all malignancies arising from the peripheral nervous system (from Schwann cells or multipotent cells of the neural crest [6,7,14,17]) or that show nerve sheath differentiation, and to replace previously heterogeneous and often confusing nomenclature such as "malignant schwannoma", "malignant neuroma", "malignant neurilemmoma", "neurogenic sarcoma", "neurofibrosarcoma", and "neurosarcoma" [14-18], for tumours of neurogenic origin and similar biological behaviour [15].

We present the second case of a patient with MPNST of the oesophagus who presented with distant metastases at the time of diagnosis which is also the second reported case with distant metastases overall. This is also the fifth case presenting with lymph node metastases (LNMs) in a total of fourteen reported cases. A final and comprehensive diagnosis was set after exploratory laparotomy and palliative surgical treatment, but the patient died 5 months after surgery with diffuse spread of the disease and this is the second reported death from this entity. Additionally, this is the first report of an oesophageal MPNST sized at less than 5 cm, with such a malignant biological and histological behaviour. Of particular interest is also the fact that the tumour was developed on ground of chronic idiopathic gastritis and active chronic and partially ulcerative oesophagitis. The report is followed by a review of the literature of the cases reported so far regarding the clinical features, diagnostic means and findings, histological parameters, treatment and prognosis.

Case report

A 76-year-old Caucasian female farmer of Greek origin with chronic gastritis was referred to a gastroenterologist due to a 3-month history of progressive dysphagia, epigastric discomfort, heartburn, fatigue and weight loss. Blood tests revealed anaemia and an oesophagogastroscopy detected a suspicious ulcerated lesion of the distal oesophagus occluding the gastro-oesophageal junction (GOJ). Ten tissue specimens were sent for histopathological evaluation. The pathology report described features compatible with a potentially aggressive GIST of possible neurogenic origin and total resection of the lesion was recommended. In the oesophageal mucosa, chronic, active and focally ulcerative oesophagitis with mild acanthosis and papilomatosis were also observed.

She was subsequently referred to our Surgical Department for further investigation and treatment. Her medical history included arterial hypertension and type 2 diabetes mellitus. Five months earlier she had undergone an abdominal Computed Tomography (CT) scan due to atypical abdominal discomfort which revealed hepatic steatosis and did not detect any other pathological findings.

On physical examination she had pale skin and mucosae and a mild tachycardia (95 bpm), and was otherwise in good condition. No abnormality was found on examination of the abdomen and respiratory system.

Laboratory tests on admission showed: Hb: 7.7 g/dl, Hct: 25%, RBC: 3.38 M/μl, MCV: 74.0 fl, MCH: 22.8 pg, WBC: 13.60 ($x10^9$/L), Neu: 87.9%, CRP: 187.7 mg/L, Glu: 164 mg/dL, γGT: 137 U/L, ALP: 177 U/L, tProt: 6 g/dL, Alb: 2.4 g/dL. No other abnormal values were observed.

Chest X-ray was normal and contrast-enhanced chest CT did not depict abnormal mediastinal lymph nodes or

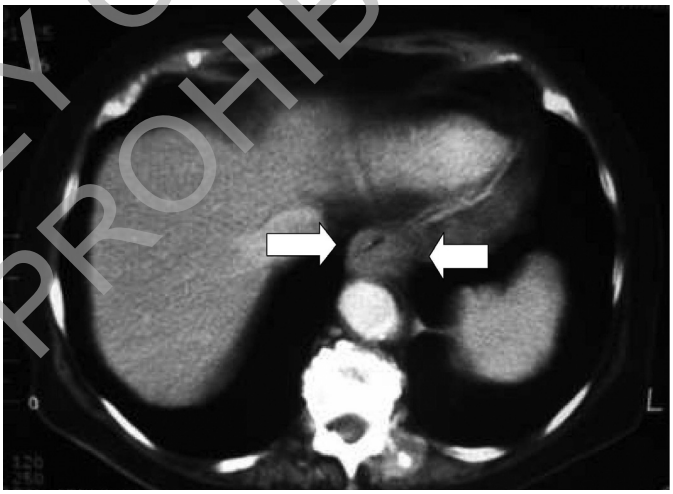

Fig. 1: Diffuse thickening of the distal oesophageal wall (arrows).

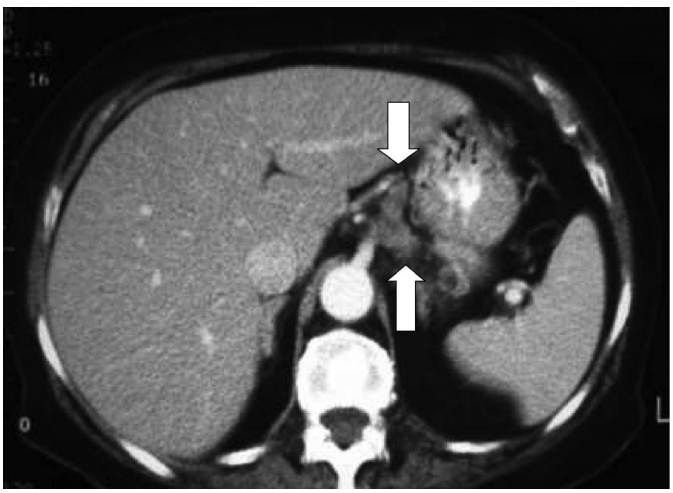

Fig. 2: Enlarged lymph nodes at the hepatogastric ligament (arrows).

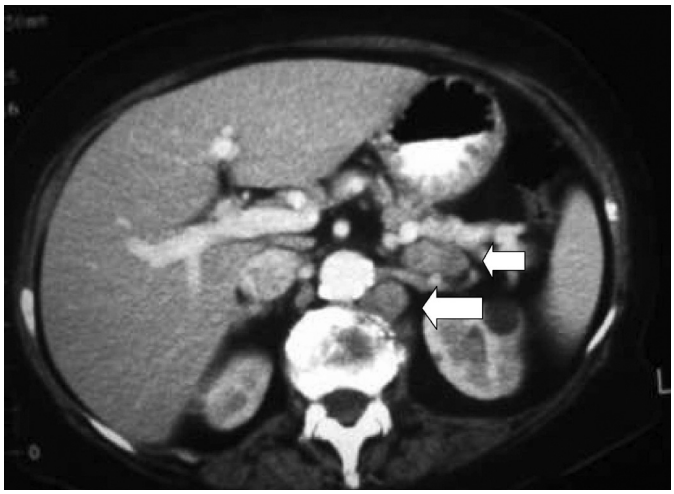

Fig. 3: A metastatic lesion of the right adrenal gland (small arrow) and an enlarged left paraortic lymph node (large arrow).

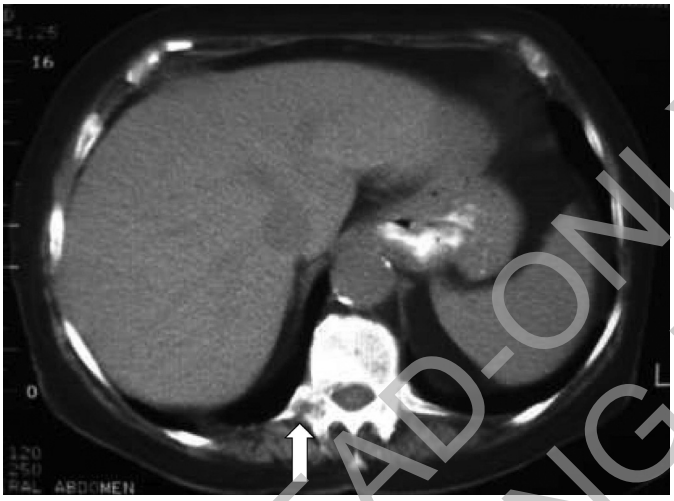

Fig. 4: Metastatic lesion of the T12 vertebra with involvement of the overlying rib (arrow).

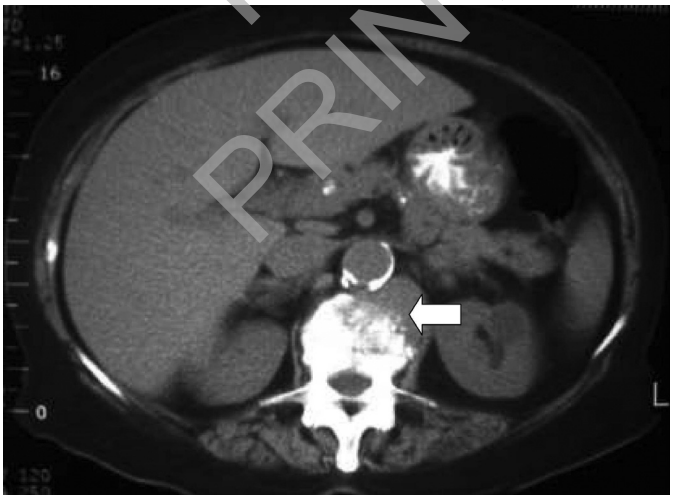

Fig. 5: Metastatic lesion of the L2 vertebra (arrow).

other pathological lesions. Contrast-enhanced abdominal/pelvic CT showed thickening of the distal oesophageal wall including the GOJ, along with enlargement of lymph nodes at the hepatogastric ligament and an enlarged left paraortic lymph node (Figs. 1, 2, 3). Secondary metastatic lesions were detected in T11, T12, L2 vertebras, ribs and left adrenal gland (Figs. 3, 4, 5). None of these findings were depicted in the abdominal CT five months earlier.

Microscopy slides from initial biopsies were further reviewed in our Pathology Department. A diagnosis of a malignant mesenchymal neoplasm of the oesophageal wall was rendered and total resection of the lesion that would enable a more thorough investigation of the neoplasm was recommended.

Initial treatment included improvement of the patient's nutritional status and transfusion of blood. An attempt for insertion of a self-expandable stent was unsuccessful due to almost complete occlusion of the oesophageal lumen by the neoplasm which did not allow further passage. Subsequently, after discussing in detail with the patient the stage of disease, prognosis and treatment options, taking into consideration the need for relief from the symptoms and mainly from progressive dysphagia which did not allow further oral intake, in association with the good performance status, the absence of a final histological diagnosis and the patient's wish to pursue palliative surgery for which she gave full informed consent, we decided to proceed with an exploratory laparotomy.

During laparotomy with a midline abdominal incision a tumour of the lower oesophagus including the GOJ and expanding to the upper stomach was seen and palpated. Enlarged regional lymph nodes could be recognised. There were no signs of metastatic spread to the solid intraabdominal organs or peritoneal surfaces. Frozen sections were sent in order to assess the histological homogeneity or heterogeneity of the tumour and with a view to obtain samples that might lead to a contributive histological diagnosis that would allow for further planning of treatment. These were positive for malignancy and described cellular features with an identical morphology as described at the previous histological report. It was clear that despite all of the so far available samples these would not suffice for a definitive diagnostic identification of the exact histological nature of the tumour that would allow accurate choice of targeted adjuvant therapies, unless the entire tumour specimen became available for examination. In view of the good general condition of the patient and the need for symptomatic relief, a clinical decision for palliative resection was made. After opening the hiatus there were not detected any enlarged mediastinal lymph nodes. A transabdominal distal oesophagectomy-total gastrectomy with regional lymphadenectomy were thus performed, and reconstruction achieved with a stapled Roux-en-Y oesophagojejunal anastomosis. The patient's recovery was uneventful, a gas-

trografin meal on the 7th postoperative day (POD) confirmed the uncomplicated function of the anastomosis, and she was discharged on the 10th POD in good condition.

Grossly at the GOJ, an ulcerated neoplasm measuring 3.9 cm in maximal diameter with a solid, grayish, rubbery cut surface was identified, expanding mainly to the oesophagus and to a lesser extend to the gastric cardia. Eight lymph nodes were retrieved from the surgical specimen. *Histological description-diagnosis:* Malignant mesenchymal neoplasm of the oesophagus with mixed pattern of spindle cells arranged in intersecting bundles (Fig. 6) and whorl formations (Fig. 7). The cells have clearly discernible boundaries, smooth edges, eosinophilic cytoplasm and basophilic, irregular nuclei, including multi-nucleated forms (Fig. 8). A striking number of mitotic figures (33/50 HPF), extensive necrotic foci and a high cellularity were also present. Immunophenotypically the neoplastic cells expressed focally S100 (Fig. 9) and NSE (Fig. 10), were positive for vimentin and bcl-2,

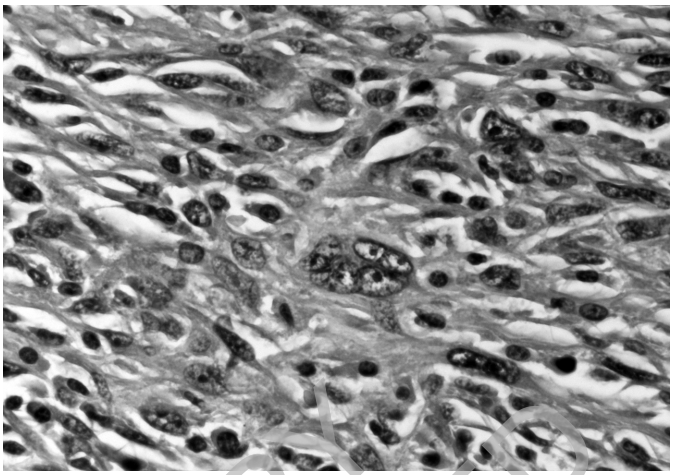

Fig. 8: (H&Ex600) Multinucleated form.

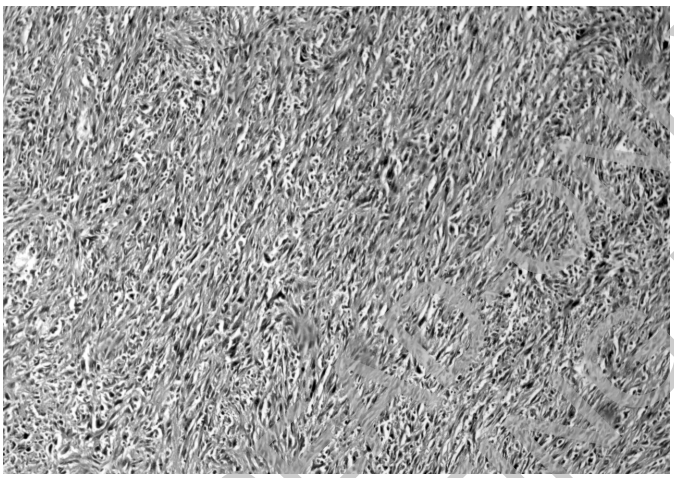

Fig. 6: (H&Ex100) Fascicular arrangement of neoplastic cells.

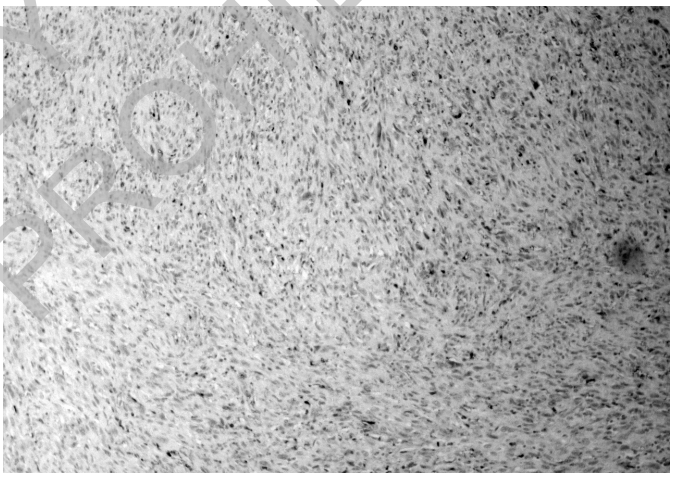

Fig. 9: (S-100x100) Focal, faint staining for S-100.

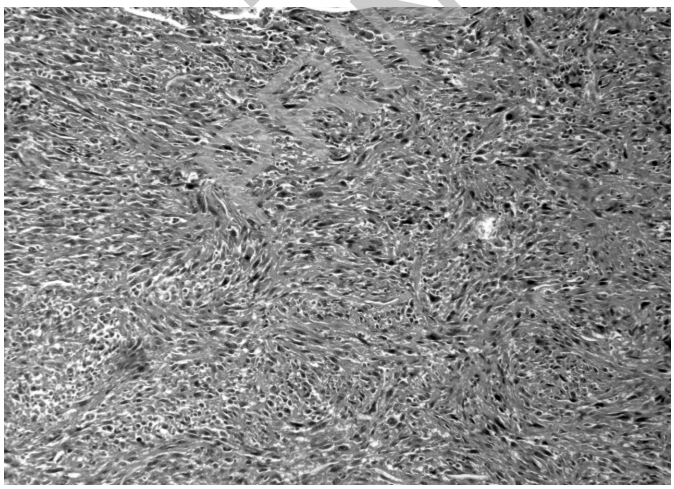

Fig. 7: (H&Ex100) Whorl formations.

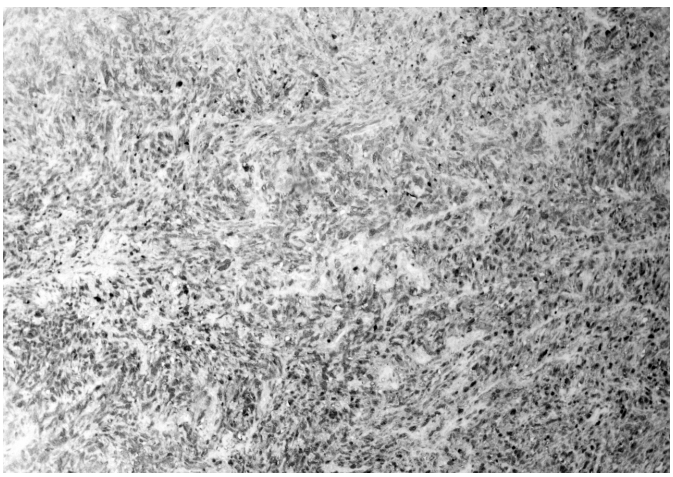

Fig. 10: (NSEx100) Positive staining for NSE.

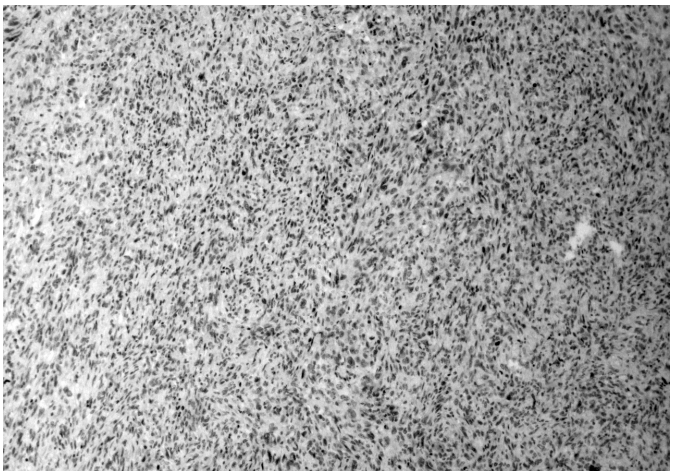

Fig. 11: (HMB45x100) Negative staining for HMB45.

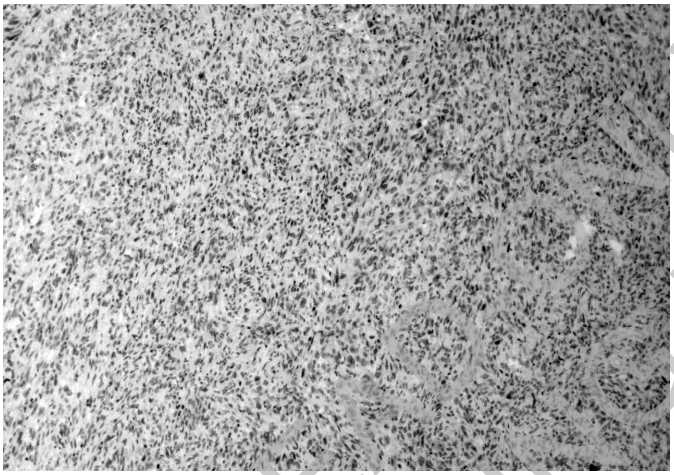

Fig. 12: (EMAx100) Negative staining for EMA.

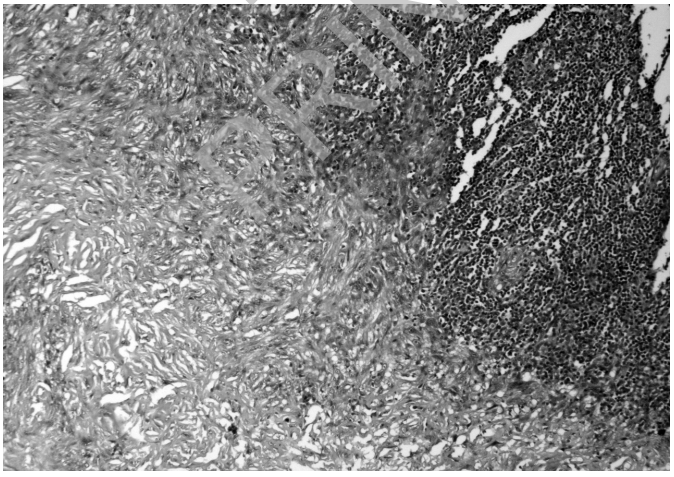

Fig. 13: (H&Ex100) Metastatic infiltration of a lymph node.

while they lacked expression of desmin, pankeratin, α-SMA, CD117, CD34, HMB-45 (Fig. 11) and EMA (Fig. 12). The concomitant expression of S-100 and NSE (underscoring the neurogenic origin of the tumour) in conjunction with lack of expression of other differentiation markers clearly suggests the diagnosis of a Malignant Peripheral Nerve Sheath Tumour. A metastatic infiltration in 2 of the 8 harvested lymph nodes was identified (Fig. 13). The proximal and distal surgical margins were clear (2.5cm free proximal margin). Additionally, chronic idiopathic gastritis with mild atrophy, an expansion of parietal cells and hyperplasia of gastrin-producing cells were observed.

The patient subsequently received postoperative chemotherapy (CMT) with doxorubicin and ifosfamide but developed rapid diffuse metastatic spread and died 5 months after surgery.

Discussion

MPNST is a rare disease accounting for 3-10% [15,17,19,20] of all soft tissue sarcomas with an incidence of 1 per 100.000 population [15,18,19]. By definition MPNST includes any sarcoma: a) originating from a peripheral nerve, b) or from a pre-existing benign nerve sheath tumour, c) or histologically demonstrating Schwann cell differentiation, d) or any malignant spindled tumour in a patient with neurofibromatosis 1 (NF-1), until proven otherwise [19,21]. Roughly up to 50% of these tumours occur in patients with NF-1 who have a 5-10% lifetime risk of MPNST [15,17-20]. However, NF-1 or 2 is not associated with gastrointestinal development of neurogenic tumours [1]. None of the patients with oesophageal MPNST had underlying neurofibromatosis [1-7,9-14]. Roughly 10% of MPNSTs are radiation-induced [19,21]. The remaining 40-50% accounts for sporadic cases [17-20]. An oesophageal localization of MPNST is extremely rare. Ours is the fourteenth reported case so far [1-7,9-14]. The results from our review of these cases are presented in Table I.

Median age was 55 years (range 20-76). Males to females ratio was 4:10. There is controversy in the literature regarding the sex preponderance of MPNSTs [15,20], however, for the so far reported 14 oesophageal cases, the prevalence of females with 71.4% is characteristic. Interestingly, the disease appears more frequently in Asia with 10 out of 14 cases (71.4%) and 7 reports coming from Japan (50%) [2,4,9-12,14].

Dysphagia was the leading symptom in most patients (78.5%) while in 3 cases an abnormal shadow on chest X-ray was the primary finding that led to further investigation.

Elevated inflammatory markers were occasionally reported [6,10]. Except from a case with slight increase of NSE [14] tumour markers were generally normal. Anaemia was occasionally present [12,14].

In two cases including ours, local underlying pathology was present. A case with Barrett's oesophagus and in our patient chronic gastritis and chronic ulcerative oesophagitis were observed. These patients had both MPNST at the distal thoracic - abdominal oesophagus.

Physical examination was generally unremarkable. One patient with MPNST of the upper oesophagus appeared with a palpable swelling on the neck, and a patient with metastatic disease had peripheral malignant lymphadenopathy and subcutaneous nodules at presentation.

Preoperative evaluation is carried out by various diagnostic means. A chest X-ray may occasionally reveal an abnormal shadow and lead to further investigation, but also may detect pulmonary metastases. Usually, the first exam is an oesophagogastroscopy which can show the tumour, its morphology and extension and allow bioptic sampling. Endoscopic ultrasonography (EU/S) offers the opportunity for biopsies and provides information about the tumour, regional lymph nodes and, occasionally, distant metastases [14]. An oesophagogram may demonstrate the location and extension of the tumour as well as prestenotic dilatation. Contrast-enhanced CT of the chest/abdomen is the classically performed modality for evaluation of the extent and stage of disease, however MRI has additionally been used in three cases [2,10,11]. MRI is considered to be the imaging technique of choice for the assessment of MPNSTs overall, however CT is superior for detection of pulmonary metastases [15,19] and has been recommended for this purpose for all patients diagnosed with MPNST [19]. PET-CT and 18-FDG-PET may also be used as highly sensitive (89%) and specific (95%) exams for differential diagnosis of benign neurogenic tumours from MPNST [19], however some authors emphasize on the high 18-FDG uptake of benign neoplasms [5,22]. In our case it was not directly accessible and was not expected to add to the available staging. Gallium-67 scintigraphy is rarely used for detection of malignant transformation of a benign neurogenic tumour to MPNST [19]. In one case of oesophageal MPNST, it did not add significant information [11]. Bronchoscopy may detect compression of the trachea or tumour invasion [13,14].

Amongst cases of oesophageal MPNST with a preoperative biopsy, the diagnosis of MPNST was stated in only two [1,6]. Initial wrong diagnoses [2,11-13], non-accurate or uncontributive diagnoses were common [10,14]. A preoperative diagnosis of MPNST is very difficult due to the complex differential diagnosis. Furthermore, for a safe and precise diagnosis each part of the neoplasm has to be histologically examined. Therefore, a final safe and accurate diagnosis can be only made after complete surgical resection.

The median size (greatest diameter) of the oesophageal MPNSTs removed was 6 cm (range, 3.9-10 cm).

The incidence of regional lymph node metastasis (RLNM) in cases of sarcoma is approximately 3% and has been correlated with the advance of tumour size and grade [23]. In patients with MPNST overall, LNMs occur in less than 10%, mainly in the setting of widespread metastatic disease, while isolated LNM is very atypical [20]. However, in 5 out of 14 patients (35.7%) with oesophageal MPNST, LNM was confirmed (histologically in 4, on imaging in another) and this might be significant information for the biological behaviour of MPNSTs located in the oesophagus, though inadequate for final conclusions due to the small number of patients. When LNM is diagnosed in patients with MPNST, it is mandatory to rule out the differential diagnoses of metastatic desmoplastic or neurotropic melanoma [20] as performed in our case with additional immunostain for HMB-45.

MPNSTs typically spread via perineural direct invasion or through haematogenous routes [19,20], with the lung being the commonest site [15,19,20] with up to 70% amongst metastatic cases [15], followed by bone and pleura [20]. Up to 77% of metastases occur in the setting of recurrent disease [15]. MPNSTs larger than 10 cm or located outside of the extremities have an increased risk of metastasis as well as tumours lacking S100 positivity [20]. Recently, IGF1R has been reported as significant predictor of metastasis or recurrence [16]. Ours is the second patient with oesophageal MPNST presenting with distant metastases at the time of diagnosis or in the course of disease overall. Metastatic lesions were detected in bones (T11, T12, L2 vertebras, ribs) and the left adrenal gland, while in a previous case, subcutaneous nodules as well as diffuse distant LNMs affecting multiple groups were noticed at initial presentation in a patient who developed brain metastases later [12].

For tumour grading, we used the French three-grade system as recommended by the FNCLCC [24] and also applied it for the purpose of our review in order to interpret the grade of 5 cases where it was not stated [3,7,9,10,12]. For tumour staging, we used the TNM tumour staging system according to the 7th edition of the AJCC [25].

The tumour resected at our hospital is the only grade III oesophageal MPNST so far, with a gross size less than 5 cm (3.9 cm).

Entities that should be meticulously excluded prior to the diagnosis of a MPNST include cellular schwannoma particularly in low-grade cases, synovial sarcoma, fibrosarcoma, leiomyosarcoma, melanoma (especially in cases with LNM) and clear cell sarcoma [7,15,20,21]. An appropriate immunohistochemical investigation to rule out the possibility of melanoma is mandatory, as in our case especially in the light of a LNM [20]. An absent staining with two melanocytic markers such as HMB-45 and S100 should suffice to eliminate this diagnostic possibility (our case portrayed a pale staining for S100 which is consistent with its schwannian differentiation) [19,20].

Many studies have focused on prognostic factors and survival in patients with MPNST. Demographic, morphological, surgical and oncological parameters have been associated with patients' survival, however, some of the

TABLE I - *Fourteen cases of Malignant Peripheral Nerve Sheath Tumour of the Oesophagus. (continue)*

Case	Author / Year	Age (yrs) / Gender	Geographic Distribution	Leading symptom /Finding	Underlying Pathology	Location	Size (cm)	*Lymph node metastases	Distant metastases	Grade	Stage	Surgical treatment	P.O. adjuvant therapy	Available survival at the time of publication
1	Iwata (1993) [4]	56 / F	Asia	Abnormal shadow on chest X-ray	-	UpT	4.8 x 4.2 x 3.0	Absent	-	I	IA	Enucleation	-	28 months p.o., alive, disease-free
2	Morita (1996) [9]	57 / F	Asia	Dysphagia	-	UpT	4.0 x 3.5 x 2.7	Absent	-	I	IA	Enucleation +	-	24 months, p.o., alive, disease-free
3	Manger (2000) [6]	60 / F	Europe	Dysphagia	-	DisT	10.0 x 3.8 x 3.8	Absent (0/7)	-	III	III	Thoracotomy – en block partial oesophagectomy	-	48 months p.o., alive, disease-free
4	Murase (2001) [2]	49 / F	Asia	Abnormal shadow on chest X-ray	-	MidT	8.2 x 5.7 x 3.7	Present (1/2)	-	II^X	III	Enucleation +	-	16 months p.o., alive, disease-free
5	Sato (2002)[10]	55 / M	Asia	Dysphagia	-	DisT	8.5 x 7.0 x 4.0	Absent	-	I^X	IB	Enucleation	-	20 months p.o., alive, disease-free
6	Tsuji (2003)[11]	49 / F	Asia	Dysphagia / Cough	-	MidT	8.2 X 5.8 X 3.7	Present	-	n/a	III	Enucleation	-	n/a
7	Sánchez (2004) [1]	54 / M	Latin America	Dysphagia	Barrett's oesophagus	DisT-AO	6 (Gastroscopy report)	Present (3/5)	-	III	III	Ivor-Lewis oesophagectomy	-	2 months p.o., alive, disease-free
8	Basoglu (2006) [3]	54 / F	Asia	Dysphagia / Mass in neck	-	UpT	6 x 6	Absent	-	I^X	IB	Abdomino-cervical subtotal oesophagectomy	-	40 months p.o., alive, disease-free

TABLE I - *Fourteen cases of Malignant Peripheral Nerve Sheath Tumour of the Oesophagus. (continue)*

9	Kitami (2009)[12]	62 / M	Asia	Fever / Dysphagia	-	DisT	5.6 X 3.7 (CT report)	Present	Distant lymph nodes, sub-cutaneous nodules, brain	II / III[X]	IV	-	CMT - RT	Death 12 months post presentation
10	Davydov (2010) [13]	20/F	Europe	Dysphagia	-	UpT	8.8 x 3.0 x 3.5	Absent	-	I	IB	Enucleation	-	36 months p.o., alive, disease-free
11	Wang (2011) [5]	44 / F	Asia	Dysphagia	-	DisT	5.5 x 4.0 x 4.5	Absent	-	I	IB	Enucleation +	-	6 years p.o., alive, disease-free
12	Teshima (2012) [14]	64/F	Asia	Abnormal shadow on chest X-ray	-	UpT – MidT	8.0 x 7.5 x 4.0	Absent (0/7)	-	I	IB	Thoracoscopic oesophagectomy	-	24 months p.o., alive, disease-free
13	Su (2012) [7]	43 / M	Asia	Dysphagia	-	DisT	4.5 x 4.0 x 2.5	Absent	-	I[X]	IA	Enucleation	-	12 months p.o., alive, disease-free
14	Our case (2015)	76 / F	Europe	Dysphagia	Chronic gastritis / Chronic ulcerative oesophagitis	DisT-AO	3.9	Present (2/8)	Left adrenal gland, ribs, vertebras	III	IV	Palative surgery – transabdominal distal oesophagectomy-total gastrectomy	CMT	Death 5 months after palliative surgery

Legend: TableUpT, Upper thoracic oesophagus; MidT, Middle thoracic oesophagus; DisT, Distal thoracic oesophagus; AO, Abdominal oesophagus; *, perioesophageal; X, our interpretation of the available histological findings; n/a, not applicable; +, with resection of oesophageal mucosa; CMT, chemotherapy; RT, radiotherapy; p.o., postoperatively.

results remain controversial and further studies are necessary [15,17-20]. At present, even treated by multidisciplinary therapy, the prognosis of MPNST patients remains dismal [15,16,18]. The 5-year survival rates range from 20%-50% [18]. MPNSTs have the highest recurrence rate of any sarcomas [15]. In a study 80% of systemic relapses occurred within two years from their treatment [15]. Another interesting clinical feature of MPNSTs is multifocality and development of second primaries of same histology [15]. As for patients with isolated RLNM, they have an improved survival compared to those with regional and distant metastasis at diagnosis [23]. Additionally, patients with RLNM synchronous to the primary tumour have a worse prognosis than these with metachronous RLNM in the absence of distant metastasis [23]. The data from cases with oesophageal MPNST is inadequate for final conclusions, due to small number of patients and lack of long-term follow-up overall. At a median follow-up of 24 months (range 2-72), patients remained alive as well as disease-free for a median of 24 months as well, since two patients including ours were never disease-free after diagnosis and subsequently died. A study of 24 MPNST patients not including oesophageal tumours reported a median disease-free period of 17 months and median survival period of 32 months, at a mean follow-up of 38 months [15]. Direct comparison of the above outcomes is not possible, since follow-up of oesophageal MPNSTs is incomplete. It can be argued though that since 12 out of 14 patients were disease-free at the time of last follow-up, actual disease-free survival and overall survival are expected to be higher than the presented numbers and thus disease-free survival is expected to be higher compared to non-oesophageal MPNSTs. As far as overall survival is concerned, no conclusion can be drawn, yet it seems reasonable to hypothesize that a prolonged disease-free survival would possibly lead to a longer overall survival. During postoperative follow-up two patients died (13.3%) due to wide metastatic spread. Our case is the second reported death from oesophageal MPNST so far. The course of disease in our case was impressively aggressive considering the absence of any signs at abdominal CT 5 months earlier and the rapid evolution to stage IV at diagnosis until final fatal outcome 5 months after surgery, despite treatment with CMT. In addition such an aggressive evolution is remarkable and uncommon for a tumour of less than 5 cm in size. Another case has reported aggressive presentation with diffuse distant LNM and subcutaneous nodular metastases at diagnosis. This patient was initially treated with a small course of CMT and subsequent courses or radiotherapy (Rx) for two months resulting in initial decrease of the primary tumour size, however, distant metastatic disease expanded further, the patient subsequently developed brain metastases and finally died 12 months after initial presentation [12]. None of the remaining 12 patients was reported to have relapsed [1-7,9-11,13,14]. Other than that, it can be suggested that absence of LNM and distant metastasis, complete surgical resection and possibly female gender could be favourable prognostic factors. Given the extremely low frequency of this entity, it is still not possible to determine the outcome with certainty and concentration of further information is necessary [1,12,14].

Radical surgical resection is the treatment of choice for MPNSTs overall and is required for cure [15,17-20]. Most authors of oesophageal MPNSTs also agree with this approach especially when evidence or suspicion of malignancy exists preoperatively [1,3-7,12,13,14]. The surgical approach should be individualised according to the location of the tumour in the oesophagus and the extent of disease. A 2-3 cm free surgical margin should be ensured. Frozen sections may be helpful in detecting possible malignancy and examining the surgical margins. However, 8 cases were treated by surgical enucleation with satisfactory outcomes and absence of recurrence at the time of publication [2,4,5,7,9-11,13], including a case with 6 years disease-free available survival [5]. Regional lymph node dissections are not routinely performed in the management of MPNST [15,20]. Most authors agree that in patients with oesophageal MPNST, all suspected regional lymph nodes should be removed for histological examination [1,2,5,6,13,14] and this obviously applies for evident RLNM [6,13,14]. Whether standard regional lymphadenectomy should be applied for patients with oesophageal MPNST, is a question to which a positive answer seems reasonable, in the context of presence of RLNM/Ms in 5 (35.7%) of the hitherto 14 published cases, unless future evidence points to the contrary. In unresectable or metastatic cases, the treatment should be individualised taking into consideration the general status and comorbidity, including various options such as best supportive care, placement of self-expandable stents, palliative surgery and adjuvant therapies.

The documentation for the efficacy and role of adjuvant therapies such as Rx and CMT in patients with MPNST is limited and sometimes controversial [15,18-20]. Generally, the decision is made in accordance with tumour's size, depth, grade, stage and recurrence [15]. Rx has been shown to delay tumour recurrence, while long-term survival is usually not greatly improved [15,18-20]. CMT is used in unresectable or metastatic cases [15,18-20]. In our patient with oesophageal MPNST, postoperative combined CMT with doxorubicin and ifosphamide was administrated due to stage IV disease, but without significant benefit. In another case, initial CMT-Rx managed to reduce the primary tumour size, however, metastatic spread expanded further despite additional courses of Rx alone [12]. Recent genomic and molecular studies have focused on detecting molecular factors such as IGF1R, as new therapeutic targets for MPNSTs, with promising results [16,21].

Formal guidelines regarding postoperative follow-up strategies have not been defined [19]. Satisfactory results have been reported with a regular 3-monthly follow-up

with repeated imaging studies for a prolonged period [15,19]. The aggressive nature of these tumours, high recurrence rate in the form of local and systemic relapse or occurrence of second primary MPNSTs, as well as the fact that most systemic relapses occur within two years from initial treatment [14,15], should all be taken into account. Most authors of cases of oesophageal MPNST agree that a prolonged postoperative follow-up period should be mandatory [1-5,10,14] and we add that patients should be closely monitored with regular physical examination and imaging studies especially in cases with more aggressive macroscopic and microscopic features.

Conclusions

MPNSTs of the oesophagus are exceedingly rare; however, they should be included in the differential diagnosis of oesophageal tumours. Satisfactory results from previously reported cases should not lead to complacency because long-term follow-up is lacking and the disease may have very aggressive course as in our case. The treatment of choice is radical surgical resection, and regional lymphadenectomy should be considered due to the high occurrence of lymph node involvement so far. A definitive histopathological diagnosis is possible after totally examining the whole surgical specimen and providing differential diagnosis from other neoplasias with the use of histological and immunohistochemical criteria. The role of adjuvant therapies needs to be further studied, however a prolonged and close postoperative follow-up should be indispensable.

Riassunto

I sarcomi dell'esofago sono una patologia molto rara, ciò nonostante ne sono state descritte diverse varianti istologiche. Il tumore maligno delle guaine nervose periferiche (MPNST) dell'esofago è un tipo di sarcoma estremamente raro, con solo tredici casi registrati fino ad oggi in letteratura. Tuttavia, questa entità dovrebbe essere inclusa nella diagnosi differenziale dei tumori dell' esofago. A causa del ridotto numero di casi riportati, le informazioni riguardanti il comportamento biologico di questa neoplasia sono, ad oggi, insufficienti.
Sebbene il MPNST sia generalmente considerato un tumore di carattere aggressivo, con alti tassi di recidiva dopo trattamento chirurgico e prognosi infausta, in precedenti casi a localizzazione esofagea sono stati riportati risultati nel complesso soddisfacenti, anche in seguito all'impiego di approcci terapeutici meno aggressivi come la sola enucleazione. Tuttavia non esiste un follow-up a lungo termine dei suddetti casi.
Qui riportiamo il caso di una paziente di 76 anni con MPNST dell'esofago presentatosi alla diagnosi con metastasi linfonodali e distali, che costituisce il secondo caso in assoluto con questa insolita presentazione.
Nella nostra paziente, il decorso di malattia è stato estremamente aggressivo ed ha causato la seconda morte per MPNST esofageo riportata, nella letteratura mondiale. La tomografia computerizzata eseguita 5 mesi prima dell'esordio con disfagia non aveva mostrato alcun segno di malignità mentre al momento della diagnosi erano evidenti un interessamento dei linfonodi locali e metastasi distali alle ossa ed al surrene sinistro. La valutazione istologica preoperatoria non ha portato ad una diagnosi conclusiva. La resezione chirurgica del tumore e la chemioterapia adiuvante non sono state sufficienti a controllare il decorso aggressivo della malattia, evoluta a stadio terminale e morte 5 mesi più tardi.
La nostra esperienza con questo caso denota che i buoni risultati descritti in letteratura non dovrebbero essere sopravvalutati, poiché esistono tumori con comportamento molto aggressivo che conducono rapidamente a stadio terminale di malattia.
Alla presentazione del caso clinico segue un'estesa revisione dei casi fino ad ora riportati in letteratura che mira a metterne in luce tutti gli aspetti rilevanti quali dati demografici, caratteristiche cliniche, reperti diagnostici, parametri istologici, trattamento e prognosi, nonché ad estrarre preziose ed inedite conclusioni riguardo questa rara entità. Particolare enfasi è stata posta sugli aspetti istopatologici e sulla necessità di esaminare l'intero campione chirurgico con l'impiego di metodi istologici e immunoistochimici per confermare la diagnosi. Il ruolo della terapia chirurgica è stato ampiamente riesaminato, prestando particolare attenzione al potenziale ruolo della linfoadenectomia standard nel contesto, secondo quanto riportato fino ad ora, di un'elevata incidenza di coinvolgimento linfonodale, insolita presentazione, per i sarcomi in generale ed i MPNSTs in particolare.

Acknowledgments

The authors are thankful to Dr Ryoki Arimoto and Mr Ioannis Mavroeidis for their valuable technical support.

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Commento e Commentary

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Vasileios K. Mavroeidis[1] et al. report the interesting case of a 76 y.o. female patient with malignant Peripheral Nerve Sheath Tumour of the oesophagus and a review of the pertinent literature. The authors write "Due to the small number of reported cases, the information about the biological behaviour of this entity is still insufficient". The patient underwent esophagectomy, received postoperative radiotherapy but developed rapid diffuse metastatic spread, and died 5 months after surgery. We recently wrote a similar comment for another patients who survived few months after surgery [1]. One question arises spontaneously. Should this patient have been operated, or not? A survival of only 5 months is difficult to justify after a oncologic challenging surgical case. What are the limits to perform an extended oncologic operation? Often, surgeons determine if there is the possibility of a surgical intervention using only their expertise to make decisions. Is this attitude ethical? [2-5]
I think that it is impossible to disagree with Wancata and Hinshaw who recently wrote "While both the patient's and surgeon's autonomy are a dynamic interface influencing decision making, The patient-physician relationship is one of the most deep relationship between persons. For the physician there is a desire to help patients, whereas for the patient entering into this relationship there is a need for the physician's services. An important foundation of this relationship is the principle of implicit trust; trust that the physician will do what is best for the patient [6]. Furthermore it is difficult to obtain data on long term survival in presence of "rare" diseases, and therefore as for other uncommon oncologic diseases [7,8], the need of a worldwide collaboration become mandatory to include these patients in prospective multicenter trial, otherwise their treatment remains unuseful. An ethical approach in any oncologic extended operation should probably stay in between patients' and surgeons' needs, always keeping in mind the "oath to do no harm". In the future efforts must be done to demonstrate evidence that the practice for every surgical oncologic disease is effective to prolong survival and improve quality of life.

* * *

Vasileios K. Mavroeidis 1 et al. Segnalano il caso interessante di una donna di 76 anni con un tumore maligno della guaina dei nervi periferici dell'esofago, insieme ad una revisione della letteratura pertinente. Gli autori scrivono "per il limitato numero di casi del genere segnalati, le informazioni circa il comportamento biologico di questa entità è ancora insufficiente". La paziente è stata sottoposta ad esofagectomia e radioterapia postoperatoria seguita però dal rapido sviluppo di una diffusione metastatica, ed è deceduta 5 mesi dopo l'intervento chirurgico. Abbiamo recentemente scritto un commento simile per altri pazienti che sono sopravvissuti pochi mesi dopo l'intervento [1]. Una domanda sorge spontanea: questa paziente era da operare o no? Una sopravvivenza di soli 5 mesi è difficile giustificare dopo un intervento impegnativo sul piano oncologico. Quali sono i limiti per decidere di eseguire una demolizione oncologica allargata? Spesso i chirurghi utilizzano solo la loro competenza per decidere se vi è la possibilità di un intervento chirurgico. È etico questo atteggiamento? [2-5]
Credo che sia impossibile non essere d'accordo con Wancata e Hinshaw che recentemente ha scritto "Mentre sia l'autonomia del chirurgo e quella del paziente sono un'interfaccia dinamica che influenza il processo decisionale, il rapporto medico-paziente è uno dei più profonda nella relazione tra le persone. Per il medico c'è un desiderio di aiutare i pazienti, mentre per il paziente nell'accedere a questo rapporto si trova nella necessità di poter utilizzare l'attività del medico. Un elemento fondamentale di questo rapporto è il principio della fiducia accordata; la fiducia che il medico farà ciò che è meglio per il paziente [6]. Inoltre è difficile ottenere dati sulla sopravvivenza a lungo termine in presenza di malattie "rare", e quindi come per altre malattie oncologiche non comuni [7,8], la necessità di una collaborazione a livello mondiale diventa obbligatoria per includere questi pazienti in uno studio multicentrico prospettico, altrimenti il loro trattamento rimane inutile. Un approccio etico in qualsiasi operazione oncologica radicale dovrebbe probabilmente essere ricompresa tra le esigenze dei pazienti e dei chirurghi, tenendo sempre presente il "giuramento di non nuocere". In futuro gli sforzi devono essere indirizzati per dimostrare e provare che il trattamento chirurgico per ogni malattia oncologica è efficace nel prolungare la sopravvivenza e migliorare la qualità della vita.

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Replay to the Comment

Gli Autori

The statements and queries of a bioethical nature expressed in the above commentary arose from the misunderstanding that we intended to perform an extended oncological resection; however, as has been very clearly stated in our paper, we performed an operation with palliative intent.
Also, as described in our article, our patient received chemotherapy and not radiotherapy, as suggested in the above commentary.
With regards to our clinical decision to ultimately offer palliative surgery, this was clearly very difficult to reach and was made in full consultation with the patient, and only after failure of the available endoscopic approach.
Prior to the operation, a long and in-depth discussion with the patient took place. The metastatic disease status and associated life expectancy were explained and all possible management options were explored. Following this conversation, she gave full informed consent to proceed to exploratory surgery with the aim of performing a palliative resection, to improve her symptoms and reach a final histopathological diagnosis to guide oncological therapies.
As the disease was not surgically curable and her life expectancy was unfavourable, the operation did not aim to offer an extended oncological resection of the tumour load.
As intended, good symptom control was achieved post-operatively, as well as the opportunity to offer specific tumour-targeted chemotherapy.
Due to the rarity of this entity, we completed a meticulous search of the world literature and reviewed all previously reported cases, with a view to collating all available experience regarding this tumour, to better understand its biological behavior and improve future management.

* * *

Le affermazioni e le osservazioni di natura bioetica espresse nel commento derivano dall'errata interpretazione che, nel caso descritto, si volesse eseguire una resezione oncologica estesa: come indicato in maniera esplicita nel nostro manoscritto, l'intervento da noi eseguito aveva un intento dichiaratamente palliativo.
Altro fraintendimento è che la nostra paziente abbia ricevuto, come procedura adiuvante, chemioterapia e non radioterapia, come chiaramente riportato nel nostro articolo.
La decisione ultima di perseguire una chirurgia palliativa è stata indubbiamente molto difficile, e in ogni caso presa dopo stretto consulto con la paziente, solo dopo il fallimento dell'alternativo approccio endoscopico.
Prima dell'intervento ha avuto luogo una lunga e approfondita discussione con la paziente in cui lo stato metastatico della malattia e l'aspettativa di vita associata sono stati esplicati e tutte le possibili opzioni di trattamento sono state esplorate in dettaglio. A conclusione di questa conversazione, la paziente ha dato il pieno consenso informato a procedere alla chirurgia esplorativa al fine di eseguire una resezione palliativa, ridurre i sintomi ed ottenere una diagnosi istopatologica definitiva per guidare la terapia oncologica.
Poiché la malattia non era chirurgicamente curabile e la prognosi era chiaramente sfavorevole, l'operazione non aveva lo scopo di offrire una resezione oncologica estesa del tumore.
Come da intento, dopo l'intervento, è stato raggiunto un buon controllo dei sintomi nonché la possibilità di offrire una chemioterapia oncologica mirata.
Data la rarità di questa entità nosologica, abbiamo completato una ricerca meticolosa della letteratura mondiale e rivisto tutti i casi precedentemente riportati, al fine di raccogliere tutta l'esperienza disponibile in merito a questa neoplasia, per comprenderne meglio il comportamento biologico e migliorarne la gestione futura.