Various clinical scenarios of primary melanoma of the esophagus: A retrospective 20-year analysis from two university thoracic surgery centers

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Abstract

Background. Primary melanoma of the esophagus (PME) represents a rare type of gastrointestinal malignancy with an exceptionally poor diagnosis. So far, only few descriptions of PME which satisfactorily summarize their clinical characteristics and prognosis have been published.

Objectives. The aim of our study was to summarize our experience with PME patients.

Materials and methods. In a group of 1387 patients who underwent esophagectomy due to neoplastic process in the years 2000–2020 in 2 high-volume university thoracic surgery centers, we identified those with confirmed PME diagnosis. Subsequently, their clinical characteristics, imaging and histopathological results were compared. The data regarding the long-term survival were obtained from the Polish National Death Registry.

Results. The PME was identified in 4 (0.29%) patients. Three of them (75%) were males. The mean age on admission was 64.3 ±17.5 years. The main symptom in all patients was dysphagia. In 1 patient with the most advanced PME, the clinically relevant weight loss was noted. In 3 patients, Ivor Lewis esophagectomy was performed, and 1 patient underwent McKeown resection. Histopathologic examination revealed a metastasis of lymph nodes only in 1 patient. The average maximum size of tumor was 6.9 ±4.7 cm and all tumors were located in distal part of the esophagus. Two out of those 4 patients are still alive and the longest survival time is 17 years. One patient died due to postoperative massive gastrointestinal bleeding complicated with cardiac arrest and the other one due to progression of PME systemic dissemination 6 months after surgical treatment.

Conclusions. The PME is an extremely rare diagnosis. A long-term survival can be achieved with the complete resection. Clinical scenarios of surgically treated PME patients may significantly differ.

Key words: melanoma, esophagectomy, esophageal neoplasm

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Background

Primary melanoma of the esophagus (PME) represents an exceedingly rare diagnosis.[1] Reportedly, PME concerns 0.1–0.2% of all esophageal malignancies.[1] The first histopathologically proven PME was described by Garfinkle and Cahan in 1952.[2] So far, only a few hundred such cases have been described worldwide.

Most of the evidence is based on individual case reports. Up to now, only a few series of PME patients have been described. Wang et al. described 13 PME patients treated surgically.[3] Gao et al. analyzed another Asian cohort consisting of 17 PME patients.[4] Moreover, Szumiło and Dąbrowski initially described 3 PME treated in 1 medical center.[5] However, the data of these patients were then included in the largest to date PME cohort; a significant proportion of those patients underwent molecular genetic profiling.[6]

Due to the highly unfavorable prognosis, PME is repeatedly decribed as an aggressive disease entity. As has been shown by Sabanathan et al. in their systematic review, the overall survival (OS) was only 10–13 months with a 5-year survival rate ranging from 0% to 4%. Metastatic disease was found in 40.9% of patients at the time of diagnosis. Moreover, at the time of diagnosis, more than 90% of the tumors were larger than 2 cm.[7] Similar observations also apply to the latest abovementioned cohort studies.[3–6] Wang et al. estimated the overall 1-year and 5-year postoperative survival rates as 54.0% and 35.9%, respectively.[3] Even worse treatment outcomes were reported by Gao et al. (1-year survival rate – 51%, 5-year – 10%).[4]

Objectives

We sought to analyze the incidence of PME diagnosis and long-term results of treatment in 2 Polish university thoracic surgery centers.

Materials and methods

A retrospective analysis of available data from the years 2000–2020 was conducted. The study group included consecutive patients with pathologically confirmed diagnosis of PME who underwent a curative-intent surgery. Data used for analysis were obtained from medical records. Patients' clinical and demographic characteristics, detailed histopathologic data with immunohistochemical features and imaging data were recorded, if available.[8] Finally, the data regarding the long-term survival were obtained from the Polish National Death Registry. The study protocol complied with the Declaration of Helsinki. All included patients gave informed consent. The approval of the Ethical Committee has been waived because of the retrospective character of the study, based exclusively on hospital records.

Results

We identified 1387 patients who underwent esophagectomy due to primary esophageal malignancies. From this group, only 4 (0.29%) cases of PME were identified. The graphical presentation of clinical course of these patients is shown in Fig. 1. A brief summary of their clinical

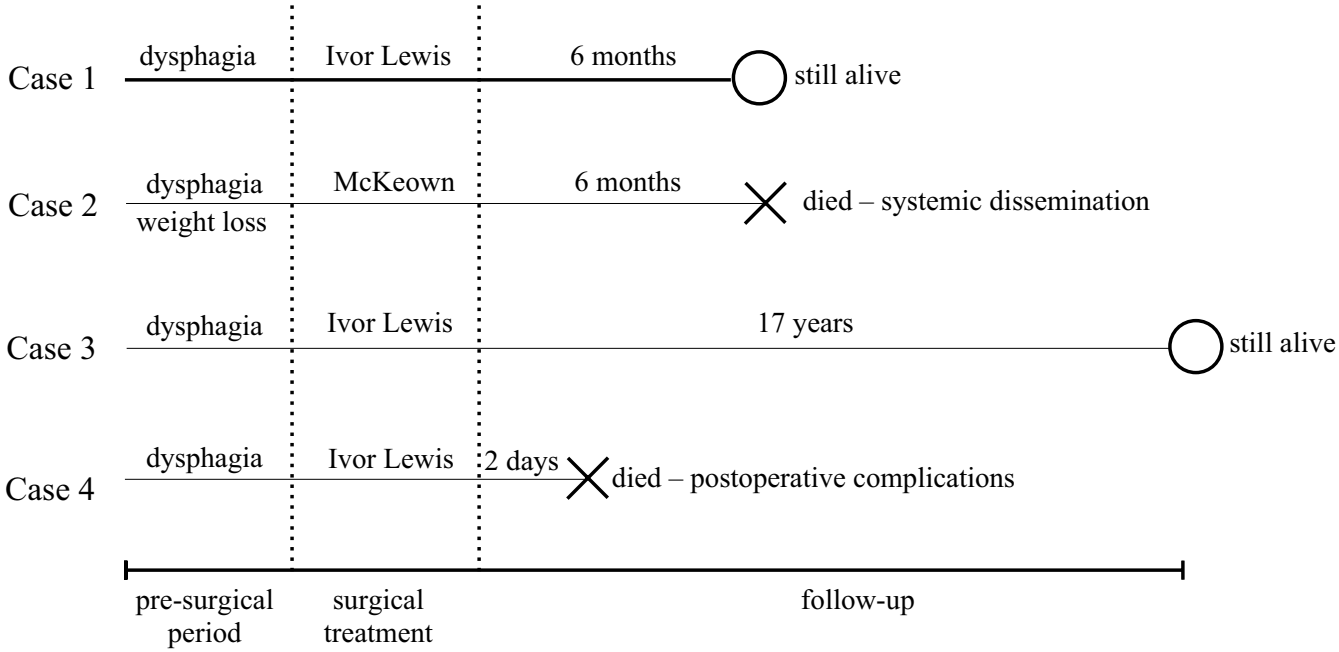

Fig. 1. The timelines presenting the clinical course of the described patients

Table 1. Clinical characteristics of the described patients with primary melanoma of the esophagus

Variable	Case 1	Case 2	Case 3	Case 4
Year	2020	2017	2003	2000
Gender	female	male	male	male
Age [years]	63	75	40	79
Symptoms	dysphagia	dysphagia, weight loss	dysphagia	dysphagia
Tumor maximum dimension [cm]	2 tumors: 2 and 3.5	13.5	7	3.5
Localization	distal	distal	distal	distal
Type of esophagectomy	Ivor Lewis	McKeown	Ivor Lewis	Ivor Lewis
Metastases in pathological evaluation	no	lymph nodes (1 paraesophageal, 1 gastric, 1 celiac)	no	no
Follow-up	alive	died after 6 months – systemic dissemination	alive	died after 2 days – postoperative complications

characteristics is presented in Table 1. As has been shown, 3 of them (75%) were males. The mean age on admission was 64.3 ±17.5 years, ranging from 40 to 79 years. All patients complained of dysphagia. In addition, in 1 patient, the clinically relevant weight loss was found (case 2).

None of the patients underwent preoperative chemo- or radiotherapy. In 3 patients, Ivor Lewis esophagectomy was performed and in 1 patient, McKeown esophagectomy was used (case 2). In all cases, surgical intervention was successful, without any perioperative complications. Histopathologic examination revealed metastasis in lymph nodes in 1 patient (case 2). The average maximum size of the tumor was 6.9 ±4.7 cm and all tumors were located in the thoracic part of the esophagus. Two patients are still alive and the longest survival time is 17 years (case 3).

Case 1

A 63-year-old female in a good general condition with symptoms of dysphagia was admitted due to previously diagnosed PME. A detailed examination of skin, mucosa and anus did not reveal any suspicious lesions. Endoscopic examination with endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) revealed a polypoid esophageal tumor at a distance of 31 cm from incisors line and thickened esophageal wall in the esophagogastric junction. The enlargement of mediastinal lymph nodes was not detected. Due to a local advancement confirmed with contrast-enhanced computed tomography (CECT) and positron emission tomography (PET), the clinical stage was estimated as cT2N0M0 (Fig. 2A,B).

The patient underwent Ivor Lewis esophagectomy with D2 lymphadenectomy and the postoperative course was uneventful.

Pathological examination confirmed the initial diagnosis and staging of PME (pT2N0M0, R0) (Fig. 2C,D). In the resected specimens, 2 separate tumors with a diameter of 2.0 cm and 3.5 cm were described. Low melanotic neoplastic cells showed features of extensive lentiginous spread. The PME invaded the mucosa and submucosa, and there were no signs of angioinvasion. The number of mitoses was about 9/mm^2. No metastases were found in any of the 32 analyzed lymph nodes.

Six months after surgery, the patient is still alive and was scheduled for further oncological treatment by the Multidisciplinary Tumor Board.

Case 2

A 75-year-old male was admitted with a large tumor of the esophagus diagnosed as PME on the basis of endoscopic biopsy performed in a regional hospital. On admission, patient presented with dysphagia and tolerated only soft diet. He had lost 15 kg of body weight in the preceding period. Detailed physical examination, including skin, oral mucosa and anus, did not reveal any suspicious lesions or lymph node enlargement. The patient smoked about 30 pack-years. There was no history of melanoma in his family.

Endoscopic examination including EBUS and EUS revealed an obstructing, amelanocytic tumor, at the distance of 25 cm from incisors line, and a massive hypoechogenic infiltration >50 mm tightly adjacent to the left main bronchus. The CECT showed a thickened esophageal wall with a maximal diameter of 68 × 52 mm, at the level of left atrium with its compression (Fig. 3A,B). The tumor expanded from aortic arch level to gastric cardia. Additionally, CECT revealed an enlarged lymph node (20 mm) in a subdiaphragmatic area and a lymph node of 7 mm in diameter near the gastric cardia. The PET revealed suspicious fluorodeoxyglucose-avid (FDG-avid) mediastinal and celiac lymph nodes. The clinical stage was established as cT3N3M0. The patient's condition was discussed by the Multidisciplinary Tumor Board and he was scheduled for primary surgical treatment.

A subtotal McKeown esophagectomy with an esophagogastric side-to-side anastomosis was performed. There were no intraoperative complications and the postoperative course was uneventful.

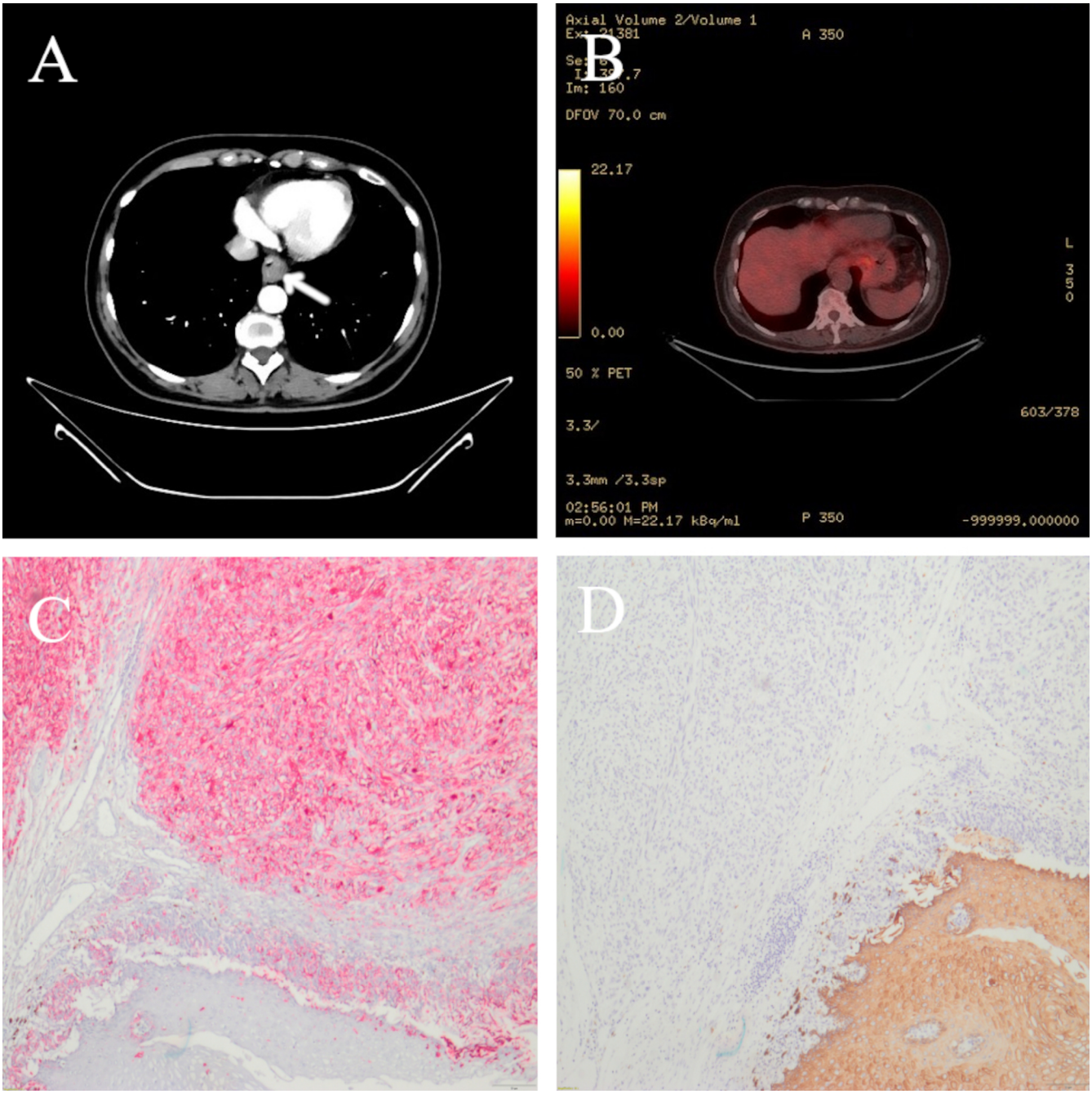

Fig. 2. Case 1. A. Contrast-enhanced computed tomography (CECT): infiltrative lesions of the esophagus wall in the lower thoracic region (15 × 37 mm) and bulky thickening of the lesser curvature of the stomach (23 × 45 mm) (arrow). Radiological features of metastases were not found; B. Positron emission tomography (PET): slight increase of 18F-fluorodeoxyglucose uptake in the lower esophagus (maximal standard unit value (SUV_{max}) 3.9) at the length of 20 mm and in the cardia and the lesser curvature of the stomach (SUV_{max} 4.4), indicating a neoplastic process (arrow); C,D. Immunohistochemical staining positive for HMB-45 protein (×200 magnification) and negative for CK AE-1/AE-3 (×200 magnification)

The pathological examination confirmed the initial diagnosis of PME (pT2N2M0, R0 resection) (Fig. 3C). Immunohistochemical staining was positive for S100 and HMB-45, and negative for cytokeratin (Fig. 3D). The BRAF V600E mutation was not found. Regional metastases were detected in 3 out of 15 resected lymph nodes: 1 paraesophageal, 1 gastric and 1 celiac.

Imaging tests performed 5 months later confirmed a single brain metastasis (25 × 20 × 20 mm) and generalized extracranial dissemination. Subsequently, the patient was scheduled for palliative stereotactic brain radiotherapy, which resulted in temporary symptomatic relief. After 6 months from surgery treatment, the patient died due to the progression of systemic dissemination.

Case 3

A 40-year-old male was admitted due to symptoms of dysphagia and suspicion of tumor of the distal part of the esophagus. On admission, the patient was in good

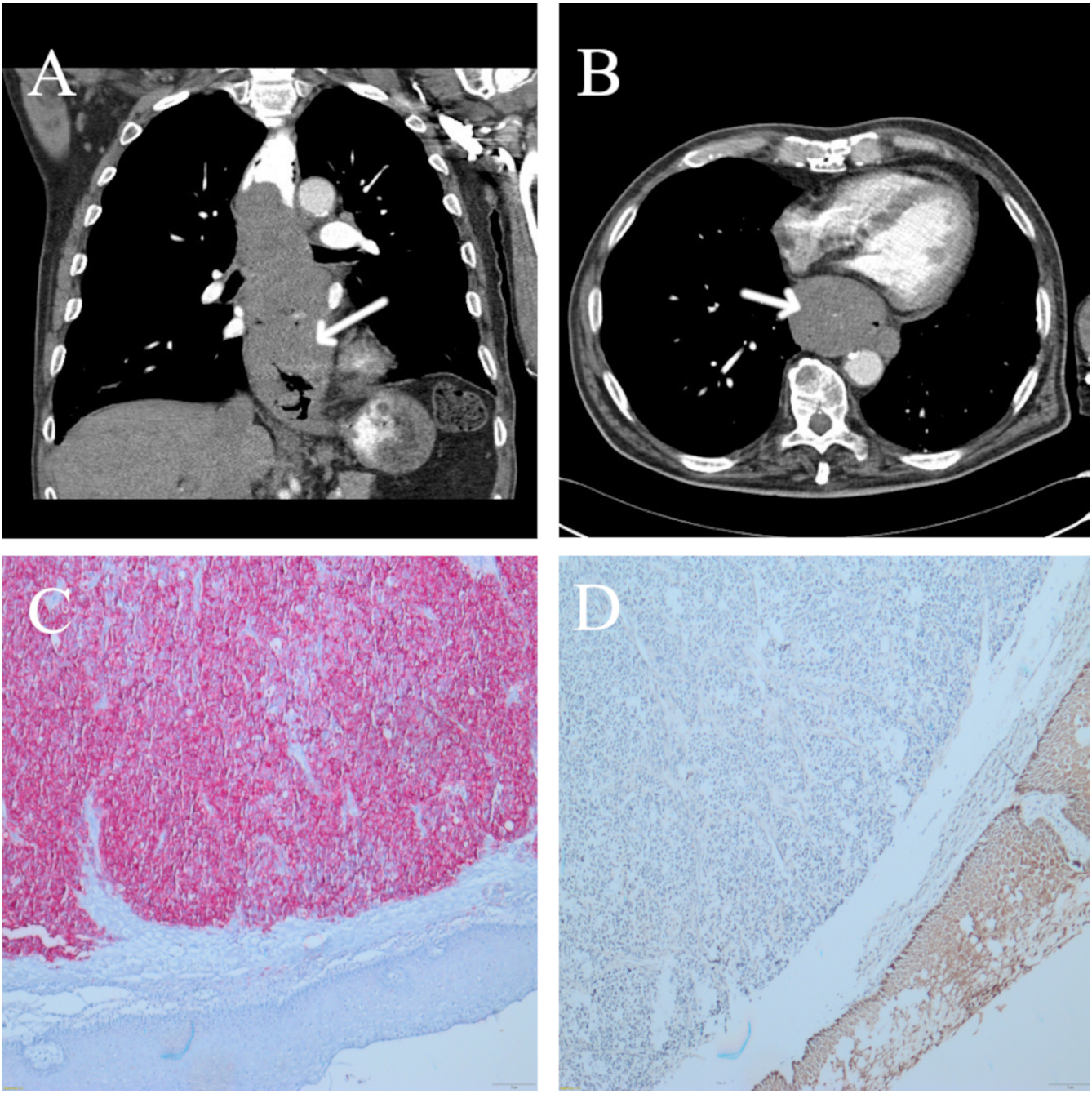

Fig. 3. Case 2. A,B. Contrast-enhanced computed tomography (CECT): polypoid tumor from the level of the aortic arch to the cardia area, with the modeling of the lower trachea, tracheal bifurcation and main bronchi (17 cm in length) (A, arrow). The largest dimensions of the esophagus were 68 × 52 mm at the level of the left atrium with its modeling and compression (B, arrow). An enlarged lymph node up to 20 mm was visualized close to the lesser curvature. Moreover, smaller paracardial lymph nodes up to 7 mm were also visible; C,D. Immunohistochemical staining positive for melanA protein (×200 magnification) and negative for CK AE-1/AE-3 (×200 magnification)

general condition, with mild symptoms of dysphagia and satisfactory tolerance of soft diet. Endoscopy with EUS revealed a polypoid tumor located 26–30 cm from the incisors line. On CECT, tumor of the distal esophagus with dimensions of 7 × 3 × 3 cm was visualized. There were no signs of enlarged lymph nodes and distal metastases. Based on those diagnostic results, the patient was scheduled for primary surgical treatment.

The Ivor Lewis esophagectomy was performed without perioperative and postoperative complications.

The pathological examination confirmed a initial diagnosis of PME. Immunohistochemical staining was positive for S100 and HMB-45, and negative for cytokeratin and desmin. The alternative diagnosis of gastrointestinal stromal tumor (GIST) was excluded by negative staining for CD117. Moreover, there were no metastases of lymph nodes.

The patient was discharged home in a good general condition. He was regularly followed up without the symptoms of PME recurrence. Currently, after 17 years since surgical treatment, he is still alive.

Case 4

A 79-year-old male with hypertension, coronary artery disease and a history of myocardial infarction 3 years before was admitted to thoracic surgery center due to the diagnosed symptomatic esophageal tumor. The general condition of the patient was good, with preserved soft diet tolerance and without any abnormalities in laboratory tests results. The CECT revealed the polypoid tumor of 3.5 cm in diameter and showed no signs of metastases (Fig. 4A,B). The patient was scheduled for primary surgical treatment.

After uneventful Ivor Lewis esophagectomy, the significant amount of fresh blood was drained through the nasogastric tube. Emergency endoscopy did not reveal the site of bleeding, and the Sengstaken–Blakemore tube was placed in surgical anastomosis. The patient required dopamine infusion, 2 units of packed red blood cells and fresh frozen plasma. On the 1st postoperative day, the patient remained stable, was extubated and required only low-flow oxygen support. On the 2nd postoperative day, asystolic cardiac arrest occurred. Resuscitation was unsuccessful.

The histopathological examination of the dissected esophagus confirmed the initial diagnosis of PME. No metastases were found in resected lymph nodes.

Discussion

Our paper is one of the very few series of PME patients published to date. In accordance with the literature data, PME was an extremely rare diagnosis among esophageal malignancies in our group. The clinical course and prognosis differed significantly in our study and depended on the baseline clinical characteristics.

Although PME is a very rare clinical diagnosis, its incidence is uncertain. Our data on PME incidence are consistent with those reported by Bisceglia et al.,[1] who estimated PME incidence as 0.1–0.2% of all esophageal malignancies.[1] In our study, based on large number of 1387 analyzed patients with esophageal malignancies, the incidence of melanomas was 0.29%.

Similarly to other papers in the field, due to limited number of patients, it is difficult to analyze their clinical profile. To compare the selected clinical features with data from literature, a brief review of selected studies is presented in Table 2.

The average patients' age at diagnosis, described in literature, ranged from 51.0 ±8.6 years to 66.4 ±7.6 years, which corresponds with our series data: 64.3 ±17.5 years. Moreover, PME is distinctly more common in males (Table 2)[3–6,9–11]; in our series, 3/4 of patients were male. The most common localization of the primary melanoma is the skin, and other less common extracutaneous sites include mucosal surfaces, uvea and retina. Primary melanoma of the gastrointestinal tract, as well as PME, are very rare. On the other hand, melanoma is one of the most common malignancies which metastasize to the gastrointestinal tract.[12] Due to this fact, the differential diagnosis between primary and metastatic melanoma may be demanding. Reportedly, the most common location of PME is the distal part of esophagus (Table 2).[3–7,9,10] This is probably due to the accumulation of melanocytes in this part of upper gastrointestinal tract.[4] In all patients in our series, the tumor was located in lower or middle thoracic esophagus.

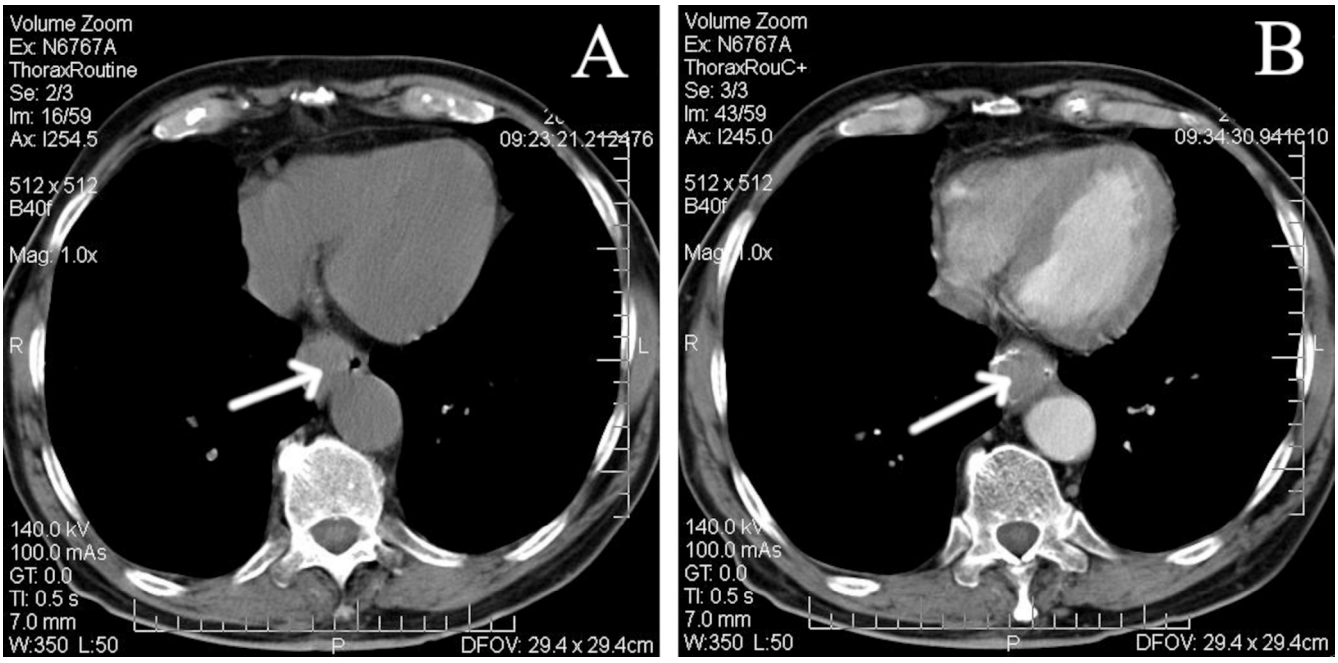

Fig. 4. Case 4. Contrast-enhanced computed tomography (CECT): infiltrative lesion in the distal part of esophagus up to 35 mm in diameter (arrows), without radiological features of metastases

Table 2. The review and summary of selected studies with primary melanoma of the esophagus patients

Study, year of publication	Number of patients	Average age [years]	Percentage of males	Distal localization [%]	Symptoms	Metastasis to lymph nodes [%]	Survival	DOPC [%]	The longest follow-up time [months]
Wang et al.[3] 2013	13	66.4 ±7.6	84.6	61.5	46.2% dysphagia, 15.4% retrosternal pain	38.5	5-year survival rate: 35.9%	0	114.1
Gao et al.[4] 2016	17	57.5 ±10.3	76.5	52.9	88.2% dysphagia, 11.76% hematemesis	52.94	5-year survival rate: 10%	5.9	204
Szumiło and Dąbrowski[5] 2011	3	54.67 ±3.21	66.67	66.67	100% dysphagia, 67% weight loss	33.33	not stated	33	20
Lasota et al.[6] 2019	20	61.05 ±10.86	70.0	65.0	87% dysphagia, 40% abdominal or chest pain, 20% weight loss	50	5-year survival rate: 12.5%	10	104
Sanchez et al.[9] 2008	5	63.4 ±15.95	40.0	60.0	100% dysphagia	75.0	median survival time: 24 months	0	36
Li et al.[10] 2007	6	51.0 ±8.6	66.67	83.33	83.33% dysphagia	66.67	median survival time: 8 months	0	17

DOPC – died of perioperative complications.

The symptoms of PME are nonspecific. The most frequently reported symptom was dysphagia, with a range of 46.2–100.0% in surgically treated PME patients.[3–6,9,10] Noteworthy, in our material, it was the main complaint in all patients. Other common symptoms related to PME expansion are weight loss and epigastric pain.[3,5,6] More severe and occasionally life-threatening symptoms such as hematemesis and melena are very rare.[4] As has been hypothesized, a softer structure of PME than other esophageal malignancies may delay the onset of symptoms and the diagnosis.[7]

Another unfavorable feature is the repeatedly reported high incidence of lymph node metastasis in pathological evaluation, with a range of 33.33–75.0% (Table 2).[5,9] Sabanathan et al. reported that one of the most common locations of metastases are the paraesophageal (10.8%) and celiac (4%) lymph nodes.[7] In our study, metastases were found only in 1 patient with the most advanced tumor, who subsequently died due to systemic dissemination (case 2). Distant metastases in PME are most commonly located in the liver.[10]

The PME is traditionally associated with the highly unfavorable long-term prognosis, which was repeatedly demonstrated in previously published studies.[1,3,4] Lasota et al. reported the observation of 16 PME patients, 2 of which died due to postoperative complications, 9 due to disease progression within 4–22 months (mean survival: 15 months) and 4 because of unknown causes within 8–104 months (mean survival: 43 months).[6] Based on the literature review, the 5-year survival rate presented in Table 2 ranged from 10% to 35.9%.[3,4] Noteworthy, only in 2 of the analyzed studies (Table 2), long follow-up, similar to that in the case of our patient who survived 17 years after surgery, was reported.[4,10] Although the prognosis is generally poor, our results show that long-term survival can be achieved with curative-intent surgical treatment.

There are no established predictive and prognostic factors in PME patients. However, as for other malignancies, one of the most important aspects is the tumor stage. Gao et al. have shown that TNM stage was the strong survival predictor for PME (hazard ratio (HR) 5.678, 95% confidence interval (95% CI): [1.125; 28.658], p = 0.0355).[4] The authors proved that patients with TNM stage III had significantly shorter postoperative overall survival than those with TNM stage I and II.[4] Another interesting aspect in the prognosis evaluation is the impact of lymph node metastasis, which was shown to be an independent prognostic factor for postoperative survival by Wang et al.[3] A similar association was shown in the previously mentioned analysis by Gao et al., but the difference was not significant.[4] Expectedly, patients with PEM have better survival than those with melanoma with metastatic involvement of the esophagus.[9]

Surgery is the treatment of choice for PME patients.[1–10] In our study, we have demonstrated that in the early stage of the disease, it is possible to achieve satisfactory treatment results (case 3). However, the role of radiotherapy and chemotherapy in the PME treatment is poorly understood.[10] Promising novel options are targeted therapy and immunotherapy. Lasota et al. conducted a precise molecular genetics profiling in a group of 15 PME cases, and found NRAS mutations in 1/3 of tumors.[6] In one of them,

KRAS p.A146T substitution was identified with acquired resistance to the dabrafenib, a BRAF inhibitor.[6,13] Due to the fact that a transmembrane receptor tyrosine kinase (KIT) has an important role in growth regulation, and in differentiation, migration and proliferation of melanocytes, its mutations were also assessed. One of the common KIT mutations associated with melanoma is juxtamembrane domain (exon 11) with p.L576P substitution.[14] It was found by Lasota et al. only in 1 patient (7%), and in 50% of tumors, KIT positivity was found. The authors also emphasized that in their study, no BRAF mutations were identified in PME.[6]

Limitations

Our study has several limitations. Firstly, it was a retrospective study based on a small group of patients. This was due to the low incidence of PME, and has been repeatedly reported by other authors. As the analyzed patients were treated over a long period of time, some imaging and histopathologic data were not available, and there was no uniform diagnostic or treatment algorithm used. Also, we did not perform specific laboratory tests which could enable further investigation of PME nature.

Conclusions

The PME is an extremely rare diagnosis with poor prognosis, but long-term survival can be achieved with surgical treatment. Clinical scenarios of surgically treated PME patients significantly differ in terms of their baseline characteristics and prognosis.

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