

CASE REPORT

Multimodal treatment of pineal metastasis from oesophageal adenocarcinoma

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Abstract

The pineal gland is a neuroendocrine gland located in the epithalamus. Primary pineal tumours are uncommon and metastatic cancer spreading to the pineal gland is even more unusual. Brain metastases from adenocarcinoma of upper gastrointestinal tract occur in less than 1.5% of patients, yet no clear data about the incidence of metastases in the pineal region are available. This study presents the case of a 73-year-old man who presented to the emergency room with neurological symptoms. MRI revealed a pathological lesion in the pineal gland with histological findings of metastasis from adenocarcinoma of gastrointestinal origin. An oesophagogastroduodenoscopy was performed and a distal lesion was found, which was biopsied and histologically defined as oesophageal adenocarcinoma. A literature search identified six articles regarding pineal metastases from oesophageal carcinoma. Our clinical case was compared to the literature cases examining, in particular, nine parameters of analysis: age, sex, histological diagnosis, timing of metastatic pineal onset, overall metastatic sites, clinical presentation, imaging

features, size and specific treatment for the pineal lesion. Despite the small sample and ‘niche’ topic in the medical literature, some important conclusions can be drawn: pineal metastases are rare, their origin is difficult to define, they require multidisciplinary management, and they can produce neurological symptoms; consequently, they must be treated through a well-timed locoregional approach (surgical or radiotherapy). Finally, further scientific research is needed to better understand the pathological mechanisms of malignant cellular homing at the pineal level.

Keywords: neuro-oncology, oesophageal cancer, pineal metastases.

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Introduction

The pineal gland is a neuroendocrine gland whose main purpose is to produce and release melatonin into the circulatory stream, necessary for the biological rhythm regulation.¹ It is located in the epithalamus, on the posterior wall of the third ventricle and, unlike other cranial structures, it lacks a well-structured blood–brain barrier.² Primary pineal tumours are uncommon, with an inci-

dence of less of 1% of all central nervous system tumours: they are typical childhood malignancies, representing 3–11% of all paediatric brain tumours, whilst the incidence in adults is low.³ Metastatic cancer spreading to the pineal gland is an even more unusual event, estimated to account for only 0.4% of central nervous system metastatic tumours.⁴ In most cases the primary tumour is localized to the lungs, but pineal gland metastases may be secondary to pancreatic, oesophageal and bladder cancers.^{5,6} Oesophageal cancer is a tumour with a

medium-to-low incidence of ~45,000 new cases/year in Europe.⁷ Men are mainly affected, with a four-fold incidence compared with women, and the average age at the diagnosis is 65 years.⁸

There are two main histotypes of oesophageal cancer: squamous carcinoma, which mainly affects the proximal part of the organ and whose main risk factors are cigarette smoking and alcoholism; and adenocarcinoma, which mainly affects the distal part and is due to obesity and gastroesophageal reflux disease. Generally, oesophageal cancer has a bad prognosis but, in recent decades, improvement of the diagnostic-therapeutic pathways has positively affected the evolution of this oncological disease.⁹ The most common sites of metastases are loco-regional lymph nodes (45%), liver (35%), lungs (20%), bones (10%), adrenal glands (5%) and peritoneum (2%).¹⁰ Brain metastases are very rare and occur in less than 1.5% of patients with upper gastrointestinal tract cancer.¹¹ Amongst brain metastases from gastrointestinal primary tumours, it is difficult to estimate the incidence in anatomical sub-sites, including the pineal region.¹²

Herein, we present a case of pineal metastasis from oesophageal adenocarcinoma managed by multimodal treatment and compare our observations with the available literature on this disease entity.

Methods

The study design includes the analysis of a case report and the subsequent review of the available literature using PubMed. According to current legislation in Italy (National Law of 30 November 2021, which regulates 'Measures aimed at facilitating and supporting the implementation of non-profit clinical trials and observational studies and the consequent legal transfer of the trials results'), de-identified case reports do not require specific approval by an ethics committee. Informed consent was obtained from the participant. Data were collected using our centre's medical records for the case report and PubMed database for the review using the term 'pineal metastases' with a search date from January 2014 to January 2024.

Case report

A 73-year-old man presented to the emergency room of Hospital Policlinico San Matteo of Pavia, Pavia, Italy, in September 2023 with neurological symptoms such as walking difficulty and retropulsion, associated with memory disorders, confusion and psychomotor slowing. A brain CT scan was performed, which documented the presence of a solid, polylobulated, hyperdense

lesion with contrast-enhanced impregnation located in the pineal gland. The lesion had 19×22×21 mm dimensions and an enlargement of the supratentorial ventricular system with periventricular hypodensity, as per trans-ependymal resorption was observed. A brain MRI with contrast medium was performed confirming the presence of the pineal lesion with contrast enhancement, traces of intralesional and perilesional bleeding, and the absence of other brain metastases (Figure 1). The patient was admitted to the neurosurgery department, where he underwent neurosurgical biopsy for pineal gland lesion and third ventriculocisternostomy endoscopic decompression.

The histological examination showed atypical glandular proliferation consistent with adenocarcinoma; immunophenotypic analysis revealed a positive profile for CK7, CDX, MUC5AC and p53, focal positivity for CK20, and negativity for S100, SATB2 and TTF1. The results suggested an adenocarcinoma of gastrointestinal origin. Oesophago-gastroduodenoscopy was then performed and a vegetating neoformation was identified at the level of the distal oesophagus/junction on which targeted biopsies were made. They were conclusive for severely atypical glands, compatible with severe dysplasia/adenocarcinoma, preserved mismatch repair status, negative HER2 (score 0) and a PD-L1 Combined Positive Score of 10 (Figure 2). It is interesting to note how the same molecular biology investigations were also conducted on the brain biopsy confirming the same molecular profile of the oesophageal tumour: HER2-negative and PD-L1 over-expressed oncological disease.

A staging total body CT scan with contrast medium in the thoracic region showed typical pathological circumferential thickening of the walls in the distal third of the oesophagus with a vegetative component in the lumen. In the mediastinal, peri-oesophageal sub-cardinal sites, in the aortopulmonary window, and in the right anterolateral paratracheal site, multiple millimetric hypervascularized lymph nodes were observed. In the abdominal region, confluent lymphadenopathies were observed near the small gastric curvature; some millimetric suspicious lymph nodes were also observed in the peripancreatic area. Vascularized nodular formations were found in the adrenal glands.

The patient's clinical case was then discussed in a multidisciplinary setting, indicating first radiotherapy of the pineal lesion followed by systemic oncological treatment, based on the general clinical picture and the biomolecular features of the tumour. The patient's medical history included active smoking and likely chronic exposure to carcinogenic substances, as he worked as a mechanic. No cases of cancer in his family were reported. He was in good general clinical condition with

Figure 1. MRI scan with the pathological lesion in the pineal region circled in red.

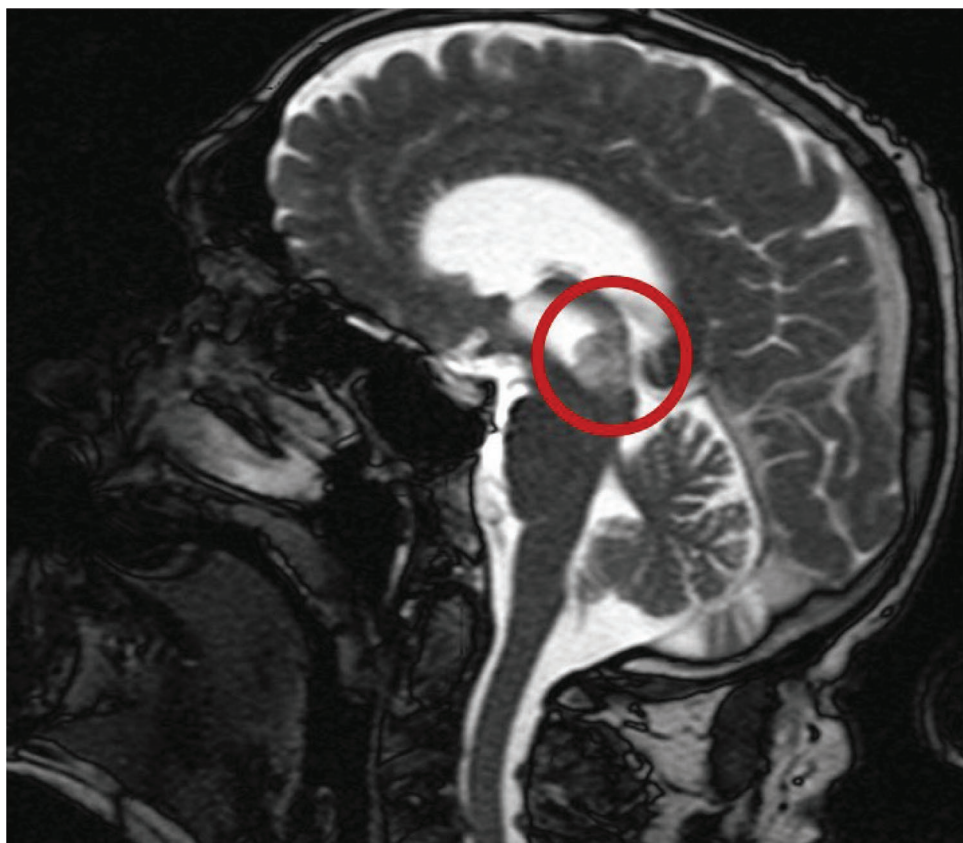
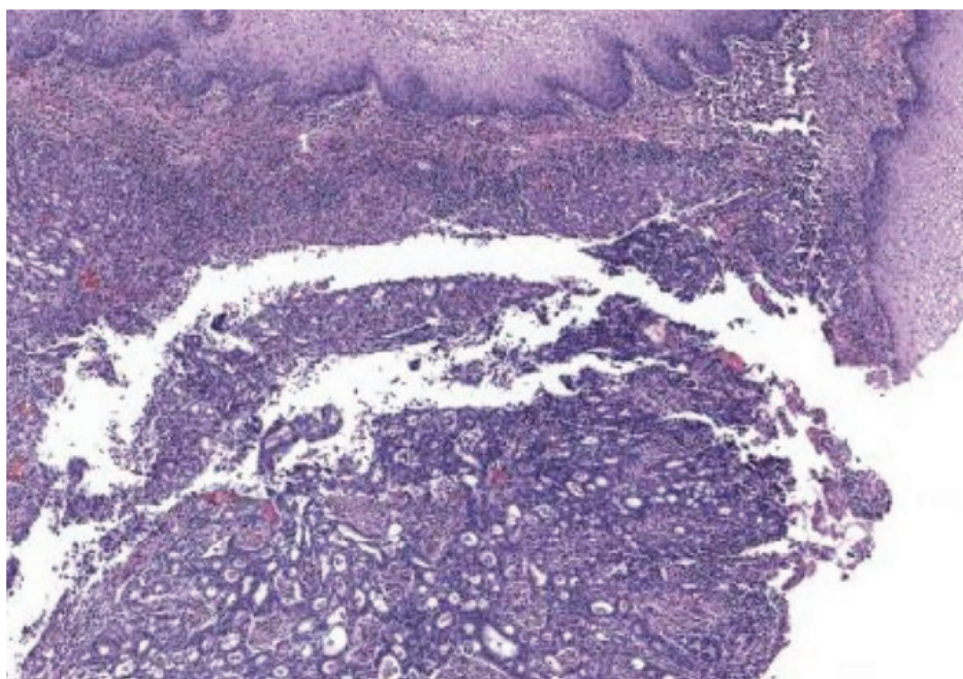


Figure 2. Oesophageal mucosal sample from primary tumour with severe dysplasia/adenocarcinoma.



ECOG-PS 0. As non-neurological symptoms, he reported dysphagia with progression of the food bolus without nausea, vomiting or gastro-oesophageal heartburn association. The patient was being treated for concomitant rheumatoid arthritis.

The oncological decision, shared with the patient, was to undertake chemo-immunotherapy treatment with the FOLFOX + nivolumab regimen, in accordance with the Check-Mate 649 trial that led to the authorization of this scheme for advanced, HER2-negative, PD-L1 over-expressed oesophageal adenocarcinoma in first-line treatment.¹³ The patient first received radiotherapy treatment to the pineal gland lesion (30 Gy in 10 fractions) and then began chemo-immunotherapy treatment (FOLFOX-5FU CI 2400 mg/mq, 5FU bolus 400 mg/mq, sodium levofolinate 200 mg/mq, oxaliplatin 85 mg/mq and nivolumab 240 mg flat dose, q14). The patient received 12 cycles of chemo-immunotherapy treatment with good overall tolerance and disappearance of dysphagia, with a mixed response pattern at the last instrumental evaluation consistent with the response criteria to immunotherapy; of particular note is the stability of the pineal lesion following radiotherapy, stability of the primary oesophageal tumour, reduction of local-regional lymphadenopathies and increase in adrenal lesions. In relation to the clinical benefit and the radiological picture, the patient will continue the oncological treatment with the maintenance phase with the De Gramont (5FU and sodium levofolinate) + nivolumab regimen. The patient underwent maintenance therapy for approximately 6 months with follow-up checks every 3 months. In October 2024, a re-evaluation CT scan showed wide disease progression in the brain, chest and abdomen, which led to severe clinical deterioration, preventing the planning of second-line oncological treatment. The patient died shortly thereafter.

Review

The pineal region is an extremely rare site of intracranial metastases, and metastases that occur in the pineal gland from oesophageal adenocarcinoma are even more unusual. Using the scientific database PubMed and performing a targeted search using the term "pineal metastases" in the last 10 years, seven publications were obtained, consisting mainly of case reports and small narrative reviews. Widening the search through the bibliography of these publications, it was possible to identify six articles regarding pineal metastases from oesophageal carcinoma.^{14–18} We analysed these cases and compared them with our clinical report.

Nine parameters of analysis were identified, namely patient age and sex, histological diagnosis, timing of metastatic pineal onset, overall metastatic sites, clinical

presentation, imaging features, lesion size and specific treatment for the pineal lesion (Table 1). Most patients were ≥60 years of age; three patients were younger than 60 years of age at diagnosis. Five cases presented in men and two in women. With regards to histological diagnosis, four cases were oesophageal adenocarcinomas, one case was a neuroendocrine carcinoma, one was a neuroectodermal tumour and for one patient the oesophageal histology was not specified. As the timing of metastatic pineal onset, only in two cases pineal lesion was present at diagnosis whilst in most cases it appeared after the diagnosis of oesophageal cancer and precisely after a median of approximately 16 months from the diagnosis. Regarding the overall metastatic sites, in four cases, the pineal region was the only metastatic site; in two cases, other metastatic sites were present, most frequently thoracic or thoraco-abdominal lymph nodes; in one case, the data are not available. All patients presented neurological symptoms consistent with obstructive hydrocephalus. With regards to the imaging features, all clinical cases were studied with contrast-enhanced MRI, which showed pineal lesions that took up contrast medium; only in one case the lesion did not take up contrast. The average size of the tumours was of ~2 cm in diameter. Finally, regarding the specific treatment for the pineal lesion, in four cases the lesion was surgically removed followed by whole-brain radiotherapy; targeted radiotherapy was performed in two cases using a local-regional technique; in one case, data are not available.

Discussion

Metastases to the pineal gland from primary oesophageal cancer are a rare event. The main objective of this work is to provide an updated review of the medical literature, starting from the analysis of a clinical case. Once the histological diagnosis is obtained, it is essential that the future management of the patient is multidisciplinary, involving a neurosurgeon, oncologist, radiotherapist and pathologist. Due to its peculiar anatomical location and the neurological symptoms that can develop, the first approach to pineal metastasis is surgical resection, when feasible, or alternatively, radiotherapy. Subsequently, the multidisciplinary team will have to establish the most appropriate systemic oncological therapy in relation to the patient's features, the oncological disease burden and the molecular biology of the tumour. In most cases, the patient presents metastatic involvement in multiple sites, and it is therefore important to perform systemic oncological treatment.

In the present clinical case, in addition to the pineal localization, the patient had lymph-nodal and adrenal

Table 1. Summary of the comparative analysis between our clinical case and the medical literature.

Features	Issues						
	Our case	Schuster et al. ¹⁴ , First case	Schuster et al. ¹⁴ , Second case	Flanagan et al. ¹⁵	Matsuda et al. ¹⁶	Blas Jhon et al. ¹⁷	Lassman et al. ¹⁸
Age	≥60 years	<60 years	≥60 years	≥60 years	≥60 years	<60 years	<60 years
Sex	Male	Male	Male	Male	Female	Female	Male
Oesophageal histotype	ADC	ADC	ADC	ADC	Neuroendocrine	Neuroectodermal	NA
Timing of pineal metastasis onset	At diagnosis	After diagnosis	After diagnosis	After diagnosis	After diagnosis	At diagnosis	After diagnosis
Overall metastatic sites	Multiple sites	Only pineal metastasis	Only pineal metastasis	Only pineal metastasis	Multiple sites	Only pineal metastasis	NA
Brain clinical presentation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MRI imaging features	CE	CE	CE	CE	No CE	CE	NA
Sizes	19 mm	18 mm	20 mm	22 mm	NA	17 mm	NA
Pineal lesion treatment	Targeted RT	Surgery and adjuvant RT	Surgery and adjuvant RT	Surgery and adjuvant RT	Targeted RT	Surgery and adjuvant RT	NA

ADC, adenocarcinoma; CE, contrast enhancement; NA, not available; RT, radiotherapy.

metastases and presented an over-expression of PD-L1; therefore, the chosen treatment was chemo-immunotherapy with the FOLFOX + nivolumab regimen. When using immunotherapy, the response criteria to this particular type of oncological treatment must be considered because of the slow latency time of the immune system and the composition of the metastatic sites in the presence of a rich inflammatory infiltrate, which produces typical radiological patterns such as pseudo-progression and mixed response.¹⁹

The medical literature on the subject is very poor and presents a series of case reports with characteristics highly similar to the case presented herein. Interestingly, most cases of oesophageal cancer metastatic to the pineal gland have a histotype of adenocarcinoma or neuroendocrine tumour, rarely squamous cell. This fact has understandably intrigued researchers who have formulated some hypotheses to understand why there is this correlation between histotype and pineal metastases. In this regard, it would seem that oesophageal adenocarcinoma cells can produce molecules belonging to the neuroserpin family that can alter the

permeability of the blood–brain barrier, allowing cells to penetrate the brain.²⁰ Another consideration, of an anatomical nature, concerns the fact that the pineal gland does not have a structured blood–brain barrier and it is also a richly vascularized region; this fact alone facilitates the spread of any malignant cells towards the brain, making it a gateway.²¹ However, the low rate of pineal metastases suggests that malignant cells generally have poor homing.²²

Conclusion

Despite the methodological limitation of a low number of patients regarding a ‘niche’ topic, our work allows us to draw some conclusions: pineal metastases are rare; their origin is difficult to define; they require multidisciplinary management; they can produce neurological symptoms; consequently, they must be treated with a well-timed loco-regional approach (surgical or radiotherapy). Finally, further research is necessary to better understand the pathological mechanisms of malignant cellular homing at the pineal level.

Contributions: FS and FR had the idea for the project. DA, AT, IM, AP, SC and DC worked on writing the clinical case. VC, FG, EB, SC, JV, AG and AV worked on the review. Finally, PP, LA and GS supervised all the work. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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