Double cystic brain metastasis in a patient with stable pancreatic intraductal papillary mucinous neoplasm

DOUBLE CYSTIC BRAIN METASTASIS IN A PATIENT WITH STABLE PANCREATIC INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

Valentina Tardivo* MD, Francesca Vincitorio* MD, Matteo Monticelli* MD, Luca Bertero° MD, Francesco Zenga* MD, Alessandro Ducati* MD, Paola Cassoni° MD, Diego Garbossa* MD PhD

* Neurosurgery Unit, Dept. Neurosciences, Città della Salute e della Scienza, University of Turin
Via Cherasco 26, 12026 Torino TO Italy

° Pathology Unit, Dept. Medical Sciences, University of Turin
Via Santena 7, 10126 Torino TO Italy

Corresponding author

Valentina Tardivo MD

Mail: tardivo.valentina@gmail.com

Address: Via Cherasco 15, 10126 Torino TO Italy

Key words

brain metastasis, IPMN, pancreatic carcinoma metastasis, cystic metastasis

Abbreviations List

CNS: central nervous system, **CUP:** cancers of unknown primary site, **IPMN**: intraductal papillary mucinous neoplasm, **PDAC**: pancreatic ductal adenocarcinoma, **US**: ultrasound, **CT**: computed tomography, **MRI**: magnetic resonance imaging, **TTF1**: thyroid transcription factor, **CK**: cytokeratin, **H&E**: hematoxylin and eosin, **FOLFOX**:5-Fluorouracil, Leucovorin and Oxaliplatin

Introduction

Brain metastasis represent the most common tumor affecting the central nervous system (CNS) and are a relatively frequent event during the course of disease for several high-incidence cancer types. Their incidence is reported to be 9%-17%, although the real frequency is thought to be higher. [1]

Despite advances in diagnostic tools and the improvement in imaging technology, a primitive tumor is not identified in up to 15% of cases of brain metastasis. [2]. Metastatic adenocarcinoma is the most common histopathology finding of cancers of unknown primary site (80%) [3, 4]. The lung is the most frequent primary site, in CNS metastases initially diagnosed as CUP however, surprisingly, a pancreatic tumor is identified in a significant number of cases (8%) while the remainder of gastrointestinal cancers represent 19%. [5].

Intraductal papillary mucinous neoplasm (IPMN), is a pathological entity first identified by Ohhashi et al. characterized by the presence of intraductal mucin-producing neoplastic epithelial cells and cystic dilation of pancreatic ducts. [6]

The malignant potential of IPMNs is low. Although IPMN is believed to progress slowly and have a better prognosis after resection compared to invasive pancreatic ductal adenocarcinoma (PDAC)[7,8], an associated invasive PDAC is found in 40%-60% of extensively sampled resected IPMNs and these cases showed a poorer prognosis compared to pure IPMN [9-11].

Here we report a patient diagnosed with IPMN that despite the stability of the pancreatic lesion developed inguinal lymph nodal and double brain metastasis. The clinical and pathological findings are discussed. Moreover, we also review all the cases of brain metastasis from pancreatic carcinoma reported in the medical literature looking for possible common features.

Materials and methods

We performed a MEDLINE and PUBMED review of the medical literature using as keywords “pancreatic neoplasms”, “pancreatic tumor” and “brain metastasis”. Only articles in English were considered and reports of post mortem discovered lesions were excluded.

The results are summarized in Table 1.

Case report

In July 2014, a 66 years old man presented with an incidental finding of a cystic lesion of the head of the pancreas after a US abdomen scan.

A CT scan showed multiple ipodense lesions of the head of the pancreas, associated with right inguinal lymphadenopathy. The pancreatic lesion was suspicious for an IPMN.

The patient underwent endoscopic biliopancreatic fine needle aspiration (FNA) of the lesion and the cytological examination showed rare papillary cellular aggregates with very bland atypia in a mucinous, Alcian blue-positive material; these findings were consistent with a possible IPMN.

Blood tests were negative for pancreatic tumor biomarkers. Esophagogastroduodenoscopy showed a normal appearing upper gastrointestinal tract. The colonoscopy detected a severe sigma diverticulosis and colorectal polyposis (histological examination showed: 2 tubular adenomas with low grade dysplasia and one tubular adenoma with high grade dysplasia).

A right lymphadenectomy was performed. The histological examination identified lymph node metastases of a mucinous papillary adenocarcinoma with bland cytological atypia (figure 2A). These findings were similar to what observed in the pancreatic FNA.

The case was discussed in a multidisciplinary panel and, since no evidence was found of other primary neoplasms, the metastases were thought to originate from a component of invasive adenocarcinoma associated to the pancreatic IPMN. Chemotherapy with the FOLFOX regimen was started, but after five cycles, a CT scan showed new abdominal lymphadenopathies, while the residual right inguinal lymphadenopathy and the pancreatic lesion were stable. A second-line chemotherapy protocol with carboplatin and taxol was then started, but only a cycle was administered because of neurologic toxicity. Therefore, the patient underwent 6 cycles of chemotherapy with gemcitabine. A follow up CT scan performed at this time-point showed stability of the pancreatic lesion, but progression of the abdominal lymphadenopathy.

In May 2017 the patient complained of bilateral worsening of visual acuity, with a severe decline of acuity for distant objects. The rest of the neuro-ophthalmologic evaluation was unremarkable. Brain MRI was performed and demonstrated two occipital bilateral cystic lesions, with no contrast enhancement, causing mass effect. (figure 1)

Patient underwent surgical removal of the brain lesions. After the craniotomy, under the dura mater it was possible to see a translucent mass. The tumor capsule was too adherent to the surrounding brain parenchyma, so it was decided to drain them first and then to dissect and remove the capsule. The content of the cysts was mucinous and transparent.

The post op was uneventful, a brain scan ruled out any acute complication and confirmed the successful removal of the lesions. Since the very first post-operative days the patient reported an improvement in visual acuity for distant objects. The patient was discharged in post-operative day 4 and died a week after for respiratory problems.

Histologic examination found a mucinous and papillary neoplasm with very mild cytological and nuclear atypia (figure 2B). Immunohistochemistry staining for cytokeratin (CK) 7 resulted strongly and diffusely positive (figure 2C), while CDX2 staining showed only a focal and faint nuclear positivity (figure 2D). Cytokeratin 20 and TTF1 were negative. These findings overlapped with the previous cytological and histological examinations, and they were deemed consistent with a pancreatic origin. [12]

Discussion

Pancreatic cancer is an aggressive neoplasm and, despite the many advances in diagnostic techniques, the majority of these tumors are identified in an already advanced, metastatic stage. Nevertheless, patients with pancreatic cancer have only very rarely been reported to develop metastatic lesions to the CNS. [13-19]

Park et al. reported only seven cases of CNS metastasis (4 cerebral-3 spinal) in a cohort of 1229 patient affected by pancreatic cancer.[15]

IPMN is a pathological entity recognized by the World Health Organization (WHO) classification of digestive system tumors in 1996 and, it is characterized by the presence of mucin-producing epithelial cells and cystic dilation in the pancreatic ducts. [6]

IPMNs represent more than one-third of all cystic neoplasms of the pancreas, but less than 1% of all pancreatic tumors [20,21]. The malignancy potential of IPMNs is low; they are categorized histologically based on the degree of dysplasia (low-grade, moderate-grade and high-grade). As

foretold, an invasive adenocarcinoma can be associated, usually of the ductal type.

Despite its more benign nature, compared to invasive adenocarcinoma, few cases of brain metastasis from IPMN are reported.

From our search we found 12 cases of brain metastasis from pancreatic tumor. The first one was reported in 1990.

In the majority of cases brain lesions were metachronous to the pancreatic cancer. Only two reports of brain metastasis secondary to IPMN-derived invasive pancreatic carcinoma.

The case presented by Chiang et all showed an immunohistochemistry pattern that was similar to our case. The only difference is that in our patient, tumor cells were focally positive for CDX 2. [19] Similarly, in the case of brain metastasis of pancreatic adenocarcinoma by El Kamar et al, the immunohistochemical stain for CK-7 was positive, while those for CK-20 and TTF-1 were negative. [16]

Only 5 out of 12 patients underwent surgical removal of the metastasis. Among them, only in one case the brain tumor was the first manifestation of the disease. In this group, the metastasis was located in the posterior cranial fossa in 3 cases. All the 5 patients received adjuvant chemotherapy. In 3/12 cases a biopsy was performed and 2/12 were treated with radiation only (whole brain radiotherapy). In 2 cases best supportive care was offered: one of them was a patient with multiple brain metastasis involving also the basal ganglia, while the other was a patient with multiple metastases at different sites at diagnosis. Only in 2 out 12 cases there were no other metastasis.

In our case, we proposed surgical resection to the patient because of the significant mass effect of the lesions and the presence of specific symptoms (visual disturbances). Moreover, even if located in an eloquent area, the metastasis were superficial and quite easy to address.

Conclusion

In our report we describe a patient that despite a pancreatic lesion, suggestive of IPMN, developed lymph nodal and brain metastasis. The pathological findings of both metastases were consistent with a pancreatic origin, despite radiological stability of the primary lesion. Therefore, despite its rarity,

pancreatic carcinoma should be included in the differential diagnosis of cerebral cystic metastasis along with lung, prostate, breast, and ovary cancers.

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Captions

Fig. 1

A-B: Pre-operative T1 with gadolinium (A) and T2 (B) MR images showing two occipital cystic lesions without significative contrast enhancement. C: Intraoperative appearence of the lesions. D: post operative CT scan showing complete removal of the lesions.

Fig. 2

A: Hematoxylin and eosin (H&E) image showing a mucinous and papillary neoplasm with mild cytological and nuclear atypia adjacent to residual lymphoreticular parenchyma; B: H&E image of the brain metastasis sample showing a mucinous and papillary neoplasm, similar to the lymph node metastasis of Figure 1A, mixed with brain parenchyma; C: Cytokeratin 7 immunohistochemistry showing a strong and diffuse cytoplasmic positivity; D: Immunohistochemistry for CDX2 showing focal and faint nuclear positivity.