Obstructive Jaundice Secondary to Pancreatic Head Metastasis of Malignant Amelanotic Melanoma as the First Clinical Manifestation

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Abstract: Malignant melanoma is commonly known for its high probability of metastasizing to distant organs. Metastases to gastrointestinal tract are well documented, but resulting jaundice is only scarcely seen. We present a case of histologically verified metastasis of amelanotic melanoma to the head of pancreas infiltrating the common bile duct and consequently causing obstructive jaundice which constituted its first clinical manifestation. Multidisciplinary approach is essential in patients with malignant melanoma since early detection of the melanoma or its metastases may improve patients' clinical outcome, especially owing to the use of targeted biological treatment without any delay.

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Introduction

Malignant melanoma is the most aggressive type of skin cancer that accounts for 4–5% of all cancers diagnosed in the USA every year and even 10.5% in Australia. Amelanotic melanoma is a histologic variant of malignant melanoma with rather discrete macroscopic appearance. The lack of melanin and therefore lack of pigmentation accounts for a low rate of early recognition by patients as well as physicians. Melanoma metastases to gastrointestinal tract are generally less common and only a few cases of metastases to the biliary tract and its surroundings have been reported. Obstructive jaundice was the first manifesting symptom in this particular patient.

Case report

A 72-years-old male patient was referred to our department by his primary care physician for jaundice that he first noticed that day. The only other complaint the patient mentioned was the presence of painless palpable subcutaneous lumps on his neck that appeared approximately two weeks before his presentation. His past medical history was significant only for an ischemic stroke 3 years prior to this admission.

The patient presented with a total bilirubin of 307.3 μmol/l (reference range 1.71 to 20.5 μmol/l), alkaline phosphatase (ALP) of 3.24 μkat/l, gama glutaryl transferase (GGT) of 5.26 μkat/l. A chest X-ray on admission disclosed moderate bilateral fluidothorax. Ultrasonography showed dilatation of intrahepatic bile ducts and common bile duct, and a hydroptic gallbladder (123 mm in longitudinal axis). A duodenoscopy demonstrated a normal looking papilla of Vater in D2 and a

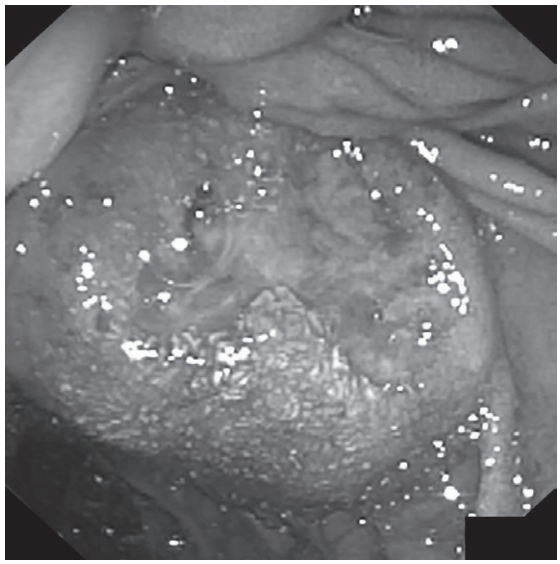

Figure 1 – Images from the duodenoscopy show the infiltration of the duodenal wall.

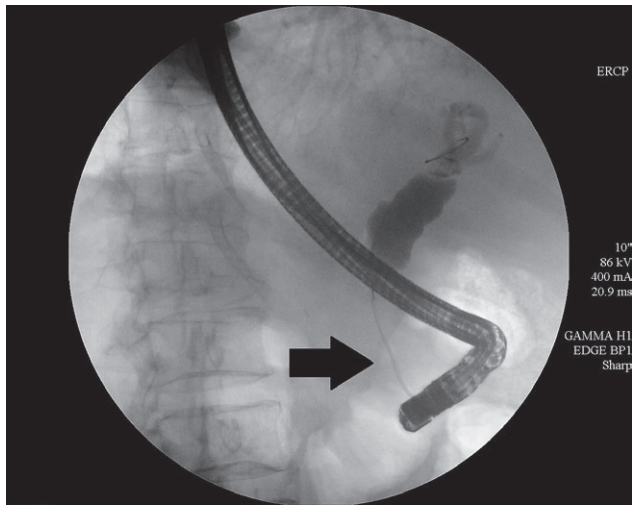

Figure 2 – An endoscopic retrograde cholangiopancreatography demonstrates a stenosis (arrow) in the common bile duct.

malignant looking polypoid mass approximately 7 cm below the papilla (Figure 1). Multiple forceps biopsies were taken solely from this mass and the papilla of Vater. No biopsies were taken from the actual lesion causing the obstruction due to high risk of bleeding. During endoscopic retrograde cholangiopancreatography (ERCP) the bile tree was cannulated, and a suprapapillary stenosis of the common bile duct in its pancreatic part was identified and stented with a 7 cm long 10 Fr plastic stent, type Amsterdam (Figure 2). The procedure was complicated by post-procedural bleeding from the papillotomy which had to be treated by intravenous fluids, vasoactive support and multiple blood transfusions in the Intensive Care Unit (ICU).

Staging CT (computed tomography) scan confirmed previous findings and showed the following: multiple metastatic lesions on the pericardium, pleura, subcutaneously in the chest wall, in the abdomen and pelvis. Other large lesions were found retroperitoneally, intraperitoneally and also in the D3 segment of the duodenum. Head of the pancreas was enlarged and had a diameter anteroposteriorly of 33 mm with a prominence towards the duodenum.

Final histopathology findings confirmed intestinal tissue with an infiltration by amelanotic malignant melanoma metastatic cells. The immunohistochemical stains for melanoma specific markers S-100 protein, SOX10, and Melan A were all positive and therefore confirmed the diagnosis of malignant melanoma (Figure 3). The bioptic tissue was also analysed for mutations in BRAF genes which could guide further targeted treatment. The mutation c. 1799T>A, p. (Val600Glu) was found in the DNA from our patient's tumour. A suspicious looking structure, a maculopapular lesion with a fibrotic pedunculated nodule in its centre with brown pigmentation of its surroundings, was identified near the left mammary gland. Therefore, it was

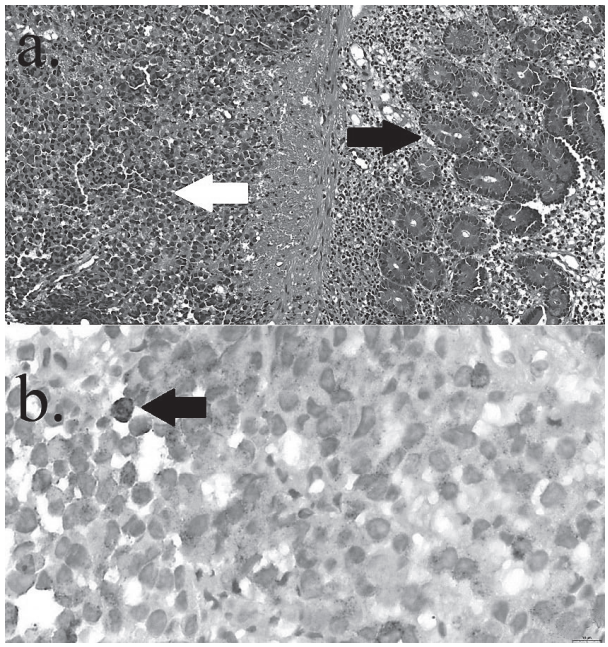

Figure 3 – Histology slides confirming the diagnosis of malignant melanoma. a) Small bowel mucosa (black arrow) with submucosal infiltration by solid epithelioid tumour with cytonuclear atypia (white arrow) (28.6×, hematoxylin and eosin and periodic acid Schiff). b) Cytoplasmic positivity of the tumour cells (arrow) for Melan-A protein (123.6× immunohistochemistry).

biopsied and subsequently examined under the microscope to identify the primary lesion. A primary tumour with histologically proven melanoma was not identified in any studied tissue samples.

The patient was informed of the unfavourable prognosis of his disease and a follow-up appointment was scheduled for after the results of BRAF mutations were expected to be available to potentially start a biologic treatment. Unfortunately, the patient died just few days later even before our scheduled appointment. Despite thorough investigation we were not able to uncover patient's place or cause of death.

Discussion

Whenever a diagnosis of melanoma is established, the most critical question is whether the cancer is localized or metastatic to regional lymph nodes or distant organs. Most deaths from melanoma are attributable to metastases that are resistant to conventional therapies (Fidler, 1990). Our patient presented with painless jaundice which was later specified as conjugated hyperbilirubinemia caused by obstruction of the biliary tract. Differential diagnosis of biliary obstruction includes among other potential causes: intrinsic and extrinsic and primary and secondary tumours of biliary ducts or adjacent organs, primary sclerosing cholangitis (PSC), cholangiopathy, acute and chronic pancreatitis, and strictures resulting from previous invasive procedures. There are 4 major types of malignant melanoma: superficial spreading melanoma,

nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. All of these types may be found in different histologic variants. One of them is the amelanotic melanoma, which is the tumour presented in this case study. Although the amelanotic melanoma is less common than the clinically pigmented melanoma, accounting for 2 to 10 percent of cases, it poses serious diagnostic challenges for patients and clinicians alike (Gualandri et al., 2009; Wee et al., 2018). This was clearly the case with our patient, who presented to the hospital with stage IV metastatic malignant melanoma. Our case is the first one to describe biliary obstruction caused by malignant melanoma metastasis to the head of pancreas. Very few other secondary tumours to the head of pancreas, such as for example multiple myeloma or diffuse large B cell lymphoma causing obstructive jaundice, have previously been described (Zheng et al., 2017; Umemura et al., 2018). Cases of malignant melanoma metastasis to the ampulla of Vater causing jaundice are the most similar to our case. These patients mostly present with signs of right upper quadrant pain with jaundice or painless jaundice with or without pruritus, as seen in our patient with the only symptom of painless jaundice. Other symptoms described in these cases include nausea, vomiting, loss of appetite and weight loss, which were not present in our patient. Majority of these patients share a poor prognosis due to disseminated stage of the disease (Parquier et al., 1991; Thompson et al., 1993; Sans et al., 1996; Van Bokhoven et al., 2006; Colovic et al., 2007; Marks et al., 2010). Malignant melanoma with gastrointestinal metastases represents a late manifestation of the disease with a generally poor prognosis (Capizzi and Donohue, 1994; Marks et al., 2010). These metastases are most commonly asymptomatic and are only discovered during an autopsy (Capizzi and Donohue, 1994; Marks et al., 2010). Finding the ideal therapy for these lesions remains difficult given the very low incidence of melanoma metastatic to the biliary tree or its surroundings (Capizzi and Donohue, 1994). Biliary stents seem to offer at least a temporary symptomatic relief with a rapid improvement of cholestasis and its clinical manifestations (Capizzi and Donohue, 1994). Surgical resection via pancreatico-duodenectomy may be an option for isolated metastatic lesions in select symptomatic patients with a good performance status, although the risk of metastatic disease leading to death still exists in these patients (Meyers et al., 1998). Our patient would have been a candidate for therapies targeting immune checkpoint molecule programmed death 1 (PD-1) or its ligand (PD-L1), cytotoxic T lymphocyte associated antigen 4 and also the mitogen-activated protein (MAP) kinase pathway with BRAF and MEK inhibitors since BRAF gene mutation was confirmed. In recent years, many potential treatment options improving median overall survival as well as quality of life were established and many more are being studied. These medicines, such as Vemurafenib, Dabrafenib, Trametinib, Nivolumab, Ipilimumab or Atezolizumab, would have been suitable treatment options in the case of our patient (Hauschild et al., 2012; Larkin et al., 2014, 2015; Swaika et al., 2014; Long et al., 2015; Robert et al., 2015; Chapman et al., 2017; Sullivan et al., 2019).

Conclusion

Multidisciplinary approach is crucial in diagnosing and establishing appropriate treatment in complex patients, as it was in our case. Malignant melanoma may present with various symptoms and therefore mimic broad spectrum of diseases. Amelanotic melanoma possesses a serious threat, not only by its lack of pigmentation and potentially delayed diagnosis, but also by its high potential to form distant metastases early in the course of the disease. A good compliance with recommended medical plan is also an important factor prolonging median overall survival.

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