Granulomatous peritoneal disease associated with oxaliplatin-based chemotherapy for ampullary adenocarcinoma: a case report

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Abstract

Adenocarcinomas of the ampulla of Vater represent only 0.2% of all gastrointestinal cancers. Due to the low incidence no large clinical trials evaluating efficacy of treatments are available. Adjuvant therapy is often administered in patients with stage IB or higher. Oxaliplatin is considered as an effective and well tolerated therapeutic option. Adverse events associated with this therapy include cardio-, neuro-, nephrotoxicity and myelosuppression. Previously granulomatous pulmonary and liver manifestations have been described in oxaliplatin-based chemotherapy. In this report peritoneal manifestation of granulomatous disease associated with oxaliplatin is described for the first time. Sarcoid-like reactions may be misinterpreted as tumour progression or metastatic disease, and may consequently result in over-treatment. (Acta gastroenterol. belg., **2023,** 86, **499-501**).

Keywords: oxaliplatin, ampullary carcinoma, chemotherapy, sarcoidosis, granulomatous disease.

Introduction

Adenocarcinomas of the ampulla of Vater (ampullary carcinomas) are located distal to the bifurcation of the distal common bile duct and the pancreatic duct. Periampullary cancers include ampullary carcinomas, carcinomas of the pancreas, distal bile duct and periampullary duodenum. Ampullary cancers represent 0.2% of all gastrointestinal cancers and 7% of all periampullary cancers (1). Due to the rarity no large clinical trials evaluating efficacy of treatments are available. Curative surgery is possible in approximately 50% of patients, however the majority of patients will eventually show disease recurrence. Patients with stage IB or higher often receive adjuvant therapy existing out of chemotherapy, sometimes combined with radiation (2). Currently there is no standard regimen of chemotherapy available. Retrospective studies from the Mayo Clinic suggest positive effect of adjuvant chemotherapy or chemoradiotherapy on overall survival and disease free survival in patients with ampullary carcinomas. Various chemotherapy regimens such as gemcitabine, FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) and FOLFORINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) were used (3,4). In locally advanced, unresectable and metastatic disease systemic chemotherapy is considered as a corner stone. Use of platinum-based chemotherapy, such as oxaliplatin, may result in various adverse effects, amongst which myelosuppression, cardio-, neuro- and nephrotoxicity (5). Granulomatous pulmonary, liver and neurologic manifestations have been described in oxaliplatin-based chemotherapy (6-9). This report describes peritoneal granulomatous manifestation associated with oxaliplatin for the first time.

Case

A 71-year old Caucasian male was referred to our Gastro-Enterology Department due to persistence of raised inflammatory values on blood analysis. The patient had a smoking history of ten pack years. He had no known exposure to tuberculosis. His medical history included the diagnosis of pT3bN1-staged adenocarcinoma of the ampulla of Vater for which a laparoscopic pylorus-resecting pancreaticoduodenectomy was performed ten months before referral. The patient received twelve doses of adjuvant chemotherapy (FOLFORINOX). The last dose was administered three months before referral.

After eight doses of oxaliplatin, the patient presented at our Gastro-Enterology Department with vague abdominal complaints and anorexia. Computed-Tomography (CT) of thorax-abdomen showed diffuse ascites, peritoneal thickening and multiple lymph nodes in mesenterial adipose tissue. These findings were not present on CT thorax-abdomen, Magnetic Resonance Imaging (MRI) and 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET-CT) at diagnosis (Figure 1, *panel A-C*). Abdominal MRI showed various mesenterial and hepatogastric lymphadenopathies, next to the previously described thickening of the peritoneum (Figure 1, *panel E-F*). Diagnostic laparoscopy with biopsy was performed and microscopical investigation showed signs of granulomatous peritonitis, malignancy was excluded in ascites and peritoneal tissue (Figure 1, *panel D and G-H*). Ziehl-Neelsen staining resulted negative and no fungi were present. Evaluating CT after 12 doses of oxaliplatin showed significant pleural effusion with pleural thickening in the basal regions

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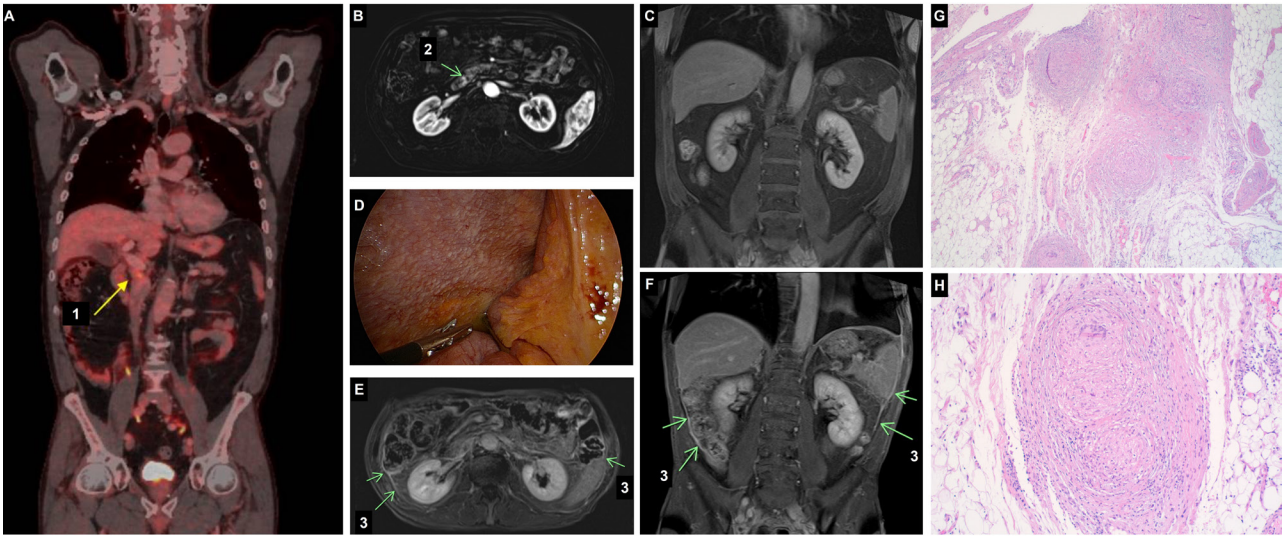

Figure 1. — Visual findings of ampullary adenocarcinoma and peritoneal granulomatous disease at diagnosis and follow-up.
(A) PET-CT performed at diagnosis of ampullary adenocarcinoma. Arrow marked by "1" indicates a hypermetabolic focus located nearby the papil of Vater. (B) MRI (axial image) performed at diagnosis of ampullary adenocarcinoma (arrow marked with "2"). (C) MRI (coronal image) performed at diagnosis shows normal peritoneal thickness, the ampullary carcinoma is not visualised. (D) Snapshot during diagnostic laparoscopy showing diffuse peritoneal lesions. (E) MRI (axial image) showing thickened peritoneum (arrows marked by "3"). (F) MRI (coronal image) showing thickened peritoneum (arrows marked by "3"). (G) Photomicrograph (magnification x40) of peritoneal granulomas (hematoxylin and eosin staining (H&E)). (H) Photomicrograph (magnification x100) of peritoneal granulomas (hematoxylin and eosin staining (H&E)).

of the lower lobe of the left lung. Microscopical and immunohistochemical evaluation of pleural fluid described chronic inflammation, signs of malignancy were absent (CK7, CK20, CDX-2 & WT1 negative).

Biochemical analysis at the moment of referral showed a raised C-reactive protein (CRP) level of 176 mg/L (reference range (RR) <5.0 mg/L) with neutrophilic leucocytosis (leucocytes 12.6x10^3/µL and 80% neutrophils; RR respectively 4.0-10.0x10^3 and 40-74%). Tumour marker CA19.9 showed a decremental trend (24.3 kU/L, compared to 41.3 kU/L 12 months before; RR <27.0 kU/L). Haemocultures were negative. CT thorax-abdomen showed mediastinal lymphadenopathies next to slight residual pleural effusion in the left lung which was previously described. Endocarditis was excluded by transthoracic and transoesophageal echocardiography. Fine needle biopsy of two mediastinal lymphadenopathies showed presence of granulomas in one node, while being absent in the other. Initially no therapy was initiated as CRP lowered spontaneously. Nonetheless raised CRP reoccurred and the patient experienced intermittent shivering and fever in following weeks. PET-CT showed no new abnormalities besides a subcutaneous hypermetabolic nodule located paramedian region of the abdomen. The nodule was surgically removed, microscopical evaluation showed no signs of malignancy nor granulomatous disease. Due to the present symptoms a trial with oral corticosteroids was initiated after which CRP normalised and fever/shivering disappeared. Steroids were slowly tapered off. Currently the patient is off steroids and asymptomatic.

Discussion

As mentioned, use of platinum-based chemotherapy may result in various adverse effects amongst which myelosuppression, cardio-, neuro- and nephrotoxicity (5). Previous authors described sarcoid-like reactions in oxaliplatin-based chemotherapy regimens (6-8). This report is, by our knowledge, the first to describe peritoneal granulomatosis associated with oxaliplatin. Sarcoidosis is a systemic inflammatory disease characterised with noncaseating granulomas. More than 90% of patients show lung manifestations, nonetheless sarcoidosis can involve any organ. Skin involvement is the most common extrathoracic manifestation of sarcoidosis. Beside mediastinal lymphadenopathies, pleural thickening and pleural fluid our patient showed no major pulmonary involvement on imaging techniques. Peritoneal granulomatous disease is considered rare. In general, histopathologic examination is necessary as definitive diagnosis cannot be made by clinical or radiological investigation alone. Determination of angiotensin-converting enzyme (ACE) levels in serum may be supporting but was not performed in our case. Awareness of sarcoid-like reactions amongst physicians is necessary as these may be misinterpreted as tumour progression or metastatic disease, which consequently may result in over-treatment. Until now, the exact etiology of sarcoidosis or sarcoid-like reactions in malignancy is unknown. Circulating tumour antigenic factors may play a significant role. Some authors mention the occurrence of sarcoid-like reactions could be a manifestation of a strong immune response to

tumour cells and may indicate favourable prognosis, however data is scarce and conflicting. Next to this, it is unclear whether the occurrence of sarcoid-like reactions may be generalised throughout various types of malignancies or therapies (10-12). Granulomatous reactions are previously described with various systemic therapies such as immune-checkpoint inhibitors, with ipilimumab as most frequently reported, and BRAF/MEK inhibitors. Other associated therapies include tumour necrosis factors-alpha inhibitors and interferons (10,11). Sarcoid-like reactions have also been described in patients receiving chemotherapy such as doxorubicin, cyclophosphamide and taxanes (13). Due to its rarity it is unclear how to optimally treat gastro-intestinal sarcoid-like manifestations (12). Previous case reports of gastro-intestinal sarcoidosis mention remission after initiation of steroids (6,14). In general steroid treatment is only indicated if associated symptoms are disabling or granulomatous disease is causing progressive organ dysfunction (12). Sarcoid-like reactions, associated with checkpoint inhibitors or oxaliplatin, in general show resolution after discontinuation of the associated agent (6-8,11).

Conclusion

Sarcoid-like reactions have been described in various malignancies and systemic therapies. Until now the exact etiological mechanism remains unknown. This is, by our knowledge, the first report describing peritoneal granulomatous disease in a patient who received oxaliplatin-based chemotherapy for ampullary adenocarcinoma. Recurrent episodes of shivering/fever and raised CRP disappeared after initiation of oral corticosteroids. Nonetheless, steroid treatment is only indicated if associated symptoms are disabling or granulomatous disease is causing progressive organ dysfunction. Spontaneous resolution is reported after discontinuation of the associated agent. Sarcoid-like reactions may be misinterpreted as tumour progression or metastatic disease, and may consequently result in over-treatment.

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