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Complicated Acute Pancreatitis Onset after Immune Checkpoint Inhibitor Treatment - A Case Report

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1. Abstract

Hodgkin lymphoma is a haematological type of cancer. Lately, immune checkpoint inhibitors (ICI) have become a part of the wide therapeutic arsenal targetting this disease. Even though they have promissing results, they are also associated with a great range of adverse events. Out of the most common, there are the gastrointestinal side effects. Among them, even if more rare compared to other organs` involvements, few acute pancreatitis cases have been previously mentioned in the literature. We present the case of a male patient known with mixed cellularity Hodgkin`s Disease Bulky disease IPS 3 who, after consecutive relapses with different therapeutic schemes, was started on Nivolumab immunotherapy. Ten months after treatment initiation, he developed the first episode of acute pancreatitis, with favorable evolution after conservative management. However, four months after, he was admitted to the emergency department with severe acute pancreatitis, complicated with pancreatic abscess. Despite all efforts, he quickly developed pulmonary embolism which, associated with a COVID-19 infection, led to exitus. ICI-associated side effects are a wide topic that still needs to be explored. The multidisciplinary team involved should consist of oncologists, internal medicine specialists, radiologists and surgeons in order to find the best management of the patient. Whether ICI should be interrupted or completely stopped depends greatly on the grade of the adverse event and on patient`s evolution.

2. Introduction

Hodgkin lymphoma (HL) affects predominantly young males aged 20-40 years old, with classical HL histology accounting for almost 95% of all HL cases [1]. The diagnostic work-up includes a combination of the presence of B symptoms (fever, night sweats, unexplained weight loss) and a plethora of imaging techniques [2]. Furthermore, the diagnosis should be immediately followed by staging, performed using the Ann Arbour classification considering defined clinical risk factors [3]. Advanced-stage HL is usually treated with chemotherapy alone, either with ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) or BEACOPP escalated (Bleomycin, Etoposide, Doxorubicine, Cyclophosphamide, Vincristine, Procarbazine, Prednisone), with a slight superiority of BEACOPP escalated for tumour control and a non-significant trend towards a better overall survival. However, the latter has increased toxicity. The treatment of relapsed HL consists of high-dose chemotherapy (HDCT), followed by autologous stem cell transplantation (ASCT) and salvage regiments with either DHAP (Dexamethasone/high-dose cytarabine/cisplatin) or Brentuximab vedotin [4]. Immune checkpoint inhibitors (ICI) represent a novel treatment option for HL patients with multiple relapses. Anti-PD-1

antibodies have shown high response rates and durable remissions in a relevant proportion of patients with disease recurrence after HDCT, followed by ASCT and Brentuximab vedotin therapy. To date, there are numerous ongoing trials for newer ICI, such as Camrelizumab, Pidilizumab, or Toripalimab, whose efficacy and safety are still being explored [5]. The fundamental reason why ICI works in HL is based on the overexpression of PD-1 and PD-2 ligands on cells that are characteristic of HL, which contributes to the enhancement of the cells' evasion of immune surveillance [6]. While ICIs have improved the survival of HL patients, the benefits have come at the cost of serious side effects known as immune-related adverse events (irAEs), which can limit cancer therapy and necessitate treatment. IrAEs manifest rarely but can be fatal. They affect different organs and cover a broad spectrum, from skin lesions to endocrine toxicity [7]. Even though they are less frequent, gastrointestinal (GI) side effects are the most commonly involved in the case of grade 3-5 irAEs [8]. Autoimmune colitis is among the most frequent and leads to severe diarrhoea which determines treatment discontinuation. However, the upper GI tract can be affected, too, manifesting with non-specific symptoms such as abdominal pain, nausea or vomiting [9]. Acute pancreatitis is a possible side effect, with few cases presented in the literature. Given their cause, treating irAEs consists of corticosteroids, an ICI-free period until symptoms recover and a potential switch to Infliximab if needed in cases of severe colitis [10].

3. Case Presentation

We present the case of a 30-year-old male patient without any relevant medical history who presented with persistent fever, without an apparent cause and rapid weight loss of 10kg in 3 months. The CT scan identified multiple bilateral pulmonary lesions, of which the largest was situated at the level of the anterior segment of the left upper lobe (LUL), with the invasion of the pleura and the subsegmental bronchioles, determining focal areas of ground-glass opacities, together with supra and subdiaphragmatic adenopathies. A biopsy was taken from the adenopathies and lung mass, with the diagnosis of mixed cellularity Hodgkin's Disease, Bulky disease IPS 3. The staging of the patient was performed according to guidelines, establishing an IVB disease with an indication of receiving 2 courses of ABVD chemotherapy. Given the lack of response, treatment was switched multiple times to the BEACOPP regimen for four cycles, then to DHAP-type rescue chemotherapy for 3 courses, with a complete response on the PET-CT. However, given the refractory course of the disease, Brentuximab Vedotin 1.8 mg/kg was initiated. The complete metabolic response was maintained until a PET-CT re-evaluation raised attention to the progressive character of the disease (Score Deauville 5). Consequently, initiating a new therapeutic line with Nivolumab (240 mg/day every 2 weeks) immunotherapy was decided. Ten months later, the patient came back to the hospital accusing abdominal pain associated with elevated pancreatic enzymes. The CT evaluation confirmed the suspicion of acute pancreatitis with a mCTSI score of 2. (Figure 1) The therapeutical decision was to stop Nivolumab and treat the pancreatic episode conservatively. Under a favorable evolution, ICI treatment was reinitiated, and the patient reached haematological remission.

Although the haematologic disease was stable under treatment, the patient had another emergency admission 4 months after the first mentioned pancreatic reaction. The CT showed diffuse pancreatic enlargement with fat stranding and an extended peripancreatic fluid collection with gas bubbles inside, suggestive of a pancreatic abscess (Figure 2). Despite antibiotic treatment and supportive care, the general state of the patient worsened, with fever, abdominal pain, a marked inflammatory syndrome and a growing abscess. Hence, he was transferred to the surgical department, where the abscess was drained laparoscopically. The following day, even if he was under antithrombotic profilaxy, he developed breathing problems that quickly escalated, with a final imaging diagnosis of pulmonary embolism (Figure 3). Moreover, a PCR test for COVID-19 infection was performed as part of the standard care and showed a positive result. After intensive care admission, he became dyspneic, tachycardic, and haemodynamically unstable. Despite all efforts to restore the fluid balance and the maximal treatment with inotropic and antiarrhythmic drugs, large-spectrum antibiotics, antivirals, monoclonal antibodies (Tocilizumab), anti-inflammatory drugs and heparin, the general state of the patient degraded and he died after one day.

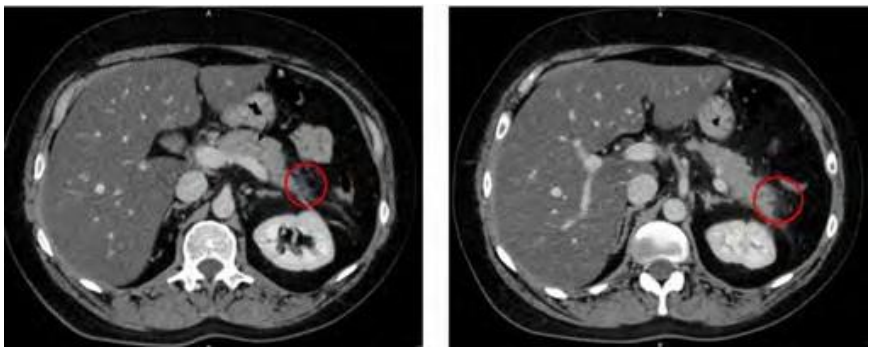

Figure 1: Axial CT (venous time), highlighting a normal-sized pancreas with discreet edematous appearance, visible Wirsung duct with normal calibre (black arrow), associating peripancreatic fat infiltration (red circles), predominantly at the corporeal and caudal level. There is no evidence of fluid collections or pancreatic necrosis on the sections at the time of the scan. mCTSI score = 2 (acute mild pancreatitis).

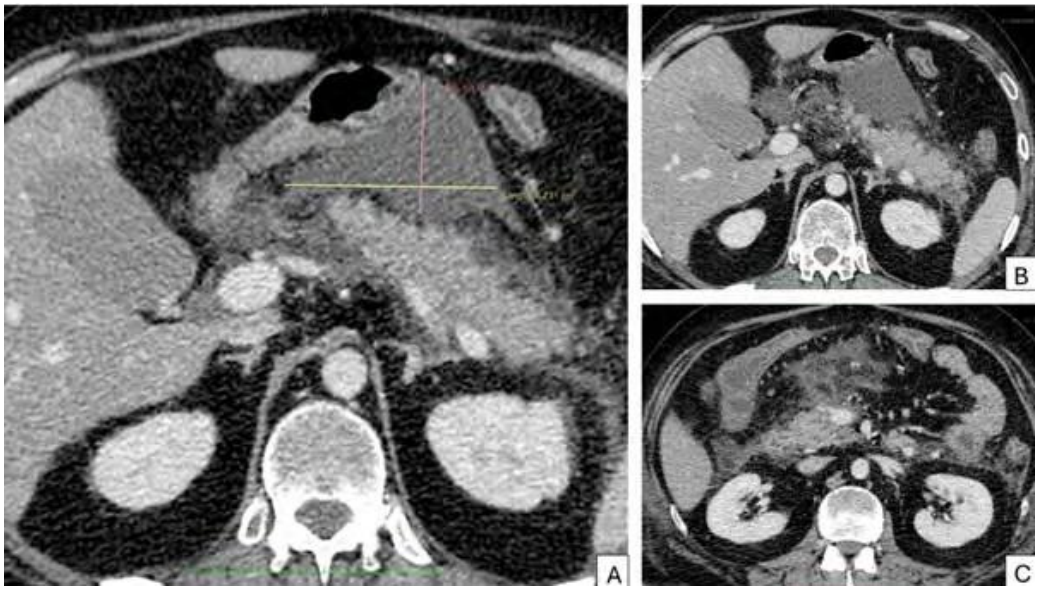

Figure 2: Abdominal CT performed in the emergency department– A. Axial section showing the formation of a collection behind the stomach, measuring ~8/5 cm; B. Axial section in venous phase demonstrating enlargement of the hypo-enhancing pancreas, with infiltration of the surrounding fat and small strands of oedema: C. Axial section showing important infiltration of the mesenteric fat, as well as smaller strands of fluid in the renal fascia and surrounding the intestinal loops.

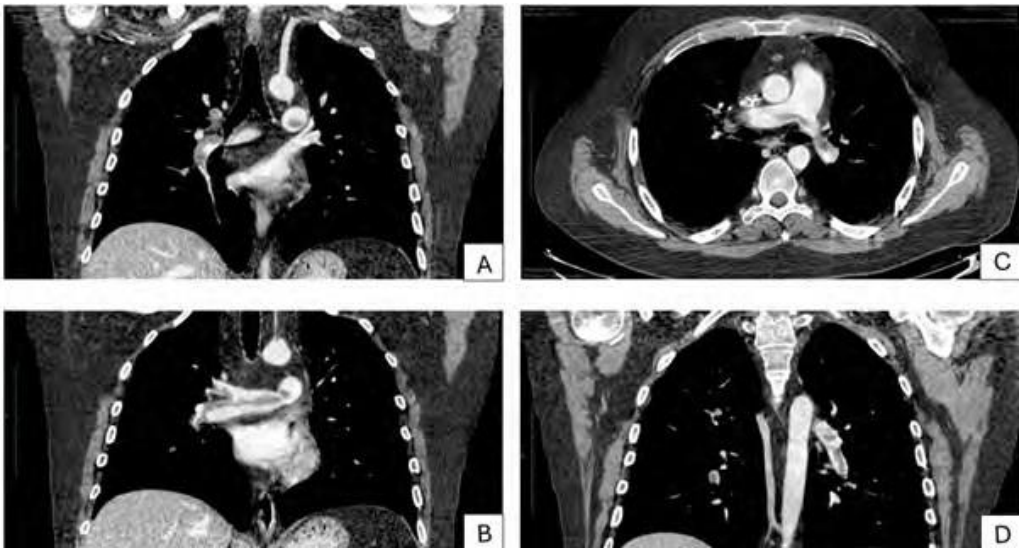

Figure 3: Pulmonary angio-CT in axial plane (C) and coronal reconstruction (A, B, D) sections demonstrate the extensive central and peripheric pulmonary thromboembolism as a filling defect at the pulmonary trunk bifurcation, extending bilaterally in the main pulmonary arteries and the segmental lobar arteries.

4. Discussions

The case particularity comes from its fluctuating evolution. The first episode of acute pancreatitis could be solved efficiently, allowing for ICI treatment continuation and remission of the lymphoma. However, it was followed by a more severe pancreatic reaction complicated with an abscess and, eventually, pulmonary embolism associated with a positive COVID test that led to exitus. There are few cases of ICI-related pancreatitis reported in the literature [11]. The presenting symptomatology is similar to the one our patient had, with epigastric pain, nausea, elevated pancreatic enzymes and an onset at different times after ICI initiation, from 8 months to 2 years. In spite of that, the evolution was different. In one case, the pancreatitis resolved itself without any treatment, while in other cases, mycophenolate mofetil, tacrolimus, or azathioprine had to be used, with some developing exocrine insufficiency following the pancreatitis. In our case, even if the initial episode could be solved, the second, more severe one, led to the death of our patient. To our knowledge, this is the first case of an ICI-related pancreatitis complicated with a pancreatic abscess ever presented in the literature. Given the continuously increasing use of immunotherapies, it is key to acknowledge their potential side effects. Recent studies showed that the incidence of irAEs is 10-15% with Nivolumab or Pembrolizumab in monotherapy, 20-30% with Ipilimumab and 55% with the combination of Ipilimumab

and Nivolumab [7]. IrAEs can affect any organ or system.(8) The mechanisms behind them are the excessive activation of T-lymphocytes and the increased ratio of CD8+/CD4+ T-lymphocytes in the peritoneal area. This leads to the destruction of pancreatic cells and a decreased endocrine and exocrine pancreatic function [12]. Upper GI involvement can be more specific to PD-1 inhibitors, such as Nivolumab, the treatment followed by our patient [13]. Even though rare, the pancreas can be the target of irAEs, with the endocrine dysfunction presenting as autoimmune diabetes [14]. However, some cases of exocrine insufficiency and acute pancreatitis following ICI therapy have been cited in the literature [15]. ICI-induced pancreatic injury (ICIPI) is an uncommon T-mediated process that is cited to appear in less than 5% of cases during ICI therapy [16]. ICIPI does not have a particular symptomatology, with its presentation ranging from asymptomatic pancreatic enzyme elevation to high-grade acute pancreatitis manifesting with severe abdominal pain. It is graded on a scale from I to V, with grade I having an amylase or lipase level of ≤ 1.5 times the upper limit of the normal (ULN), grade II >1,5-2 x ULN, grade III >2-5 x ULN, grade IV > 5 x ULN, and grade V resulting in death [17].

ICI treatment can usually be associated with elevated amylase and lipase. For this reason, in the absence of symptoms, these biological modifications remain unclear, and treatment discontinuation is not recommended based solely on them. Hence, a radiological diagnosis becomes mandatory. There have been two radiological patterns of ICI-related AP: a more common one resembling acute interstitial pancreatitis and another resembling autoimmune pancreatitis. Abdominal ultrasound shows an enlarged pancreas with uneven parenchymal echogenicity. On computed tomography examinations, the hypoenhancing pancreas is associated with increased lipid concentration and fat stranding. Magnetic resonance imaging showcases signal restriction on diffusion-weighted images and contrast enhancement in the late phase post Gadolinium administration. Supplementary, careful image analysis should focus on the differential diagnosis with potential pancreatic metastases [7]. A potential help in the follow-up could be the development of CT-based scores to forecast the outcomes of these patients, as plenty of prediction scores are being proposed in the field of pancreas imaging [18]. The management of ICI-related pancreatitis depends on its severity. For moderate episodes, NCCN recommends an interruption of ICI associated with a course of methylprednisolone or prednisolone 0,5-1 mg/kg/day. In the case of severe pancreatitis, the treatment consists of complete discontinuation of ICI and steroids 1-2 mg/kg/day [7]. After the first pancreatic reaction, our patient could continue his Nivolumab treatment. However, the second episode was more severe and did not allow ICI continuation. In the context of a frail immune system, the SARS-COV2 infection is known to be lethal. ICU admission is common among patients with dysregulated and impaired inflammatory responses, with the immunosuppression state contributing to worse outcomes [19]. In our case, the patient`s state quickly degraded as he was unresponsive to all therapeutic lines, having a heavy history of immune system disturbances.

5. Conclusion

As oncological therapies are quickly advancing, it is highly important for practitioners to know and identify irAEs as early as possible so that they can be treated accordingly.

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