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From Lipase Elevation to Diabetes – Pancreatic Involvement during Immune Checkpoint Inhibition

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Abstract

Nowadays, as a standard of care treatment of several cancers, immune checkpoint inhibitors have changed the field of oncology. However, their empowerment of T cell-mediated anti-tumor immunity bears the risk for injury of various organs as a side effect. Many years of treatment with immune checkpoint inhibitors have taught oncologists the management of common immune-related adverse events such as cutaneous, gastrointestinal, lung and cardiovascular toxicities. Nonetheless, there is still a lack of knowledge about different mechanisms, significance and management of pancreatic involvement during immune checkpoint inhibition. In this review, we examine the current evidence on lipase elevation, acute pancreatitis, diabetes mellitus and pancreatic exocrine insufficiency related to immune checkpoint inhibition. We further present approaches of diagnosis and management of these adverse events.

Keywords: Immune checkpoint inhibition, Lipase, Pancreatitis, Diabetes mellitus, Pancreatic exocrine insufficiency

Introduction

Immunotherapy has revolutionized the treatment and outcome of various malignancies. In particular, immune checkpoint inhibition (ICI) by antibodies against the checkpoints cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1) and PD ligand 1 (PD-L1) leads to augmentation of the immune response against cancer cells mediated by T cells. However, the enhanced immunity not only results in increased tumor control but often also in immune-mediated damage of other organs. These immune-related (ir) adverse event (AE)s were found to occur in about 28 - 87% of the patients treated with ICI [1,2]. The high incidence of irAEs justifies a close monitoring of patients and an extensive, routinely performed laboratory workup during ICI therapy.

Common irAEs include diarrhea, pruritus and hypothyroidism [1]. Moreover, elevation of pancreatic enzymes has been observed in many trials on ICI. A meta-analysis regarding 17197 patients receiving PD-1 inhibitor-based therapies showed that lipase elevation is one of the most common grade 3 or higher AEs [1]. Nevertheless, the clinical significance of this often high grade AE remains uncertain. Further irAEs involving the pancreas are pancreatitis as well as endocrine and exocrine insufficiency of the pancreas. Treatment with CTLA-4 antibodies with or without combination of PD-1 antibodies was shown to bear a significant risk of lipase elevation, but no significantly increased risk of pancreatitis when compared with controls [3]. Endocrine and exocrine insufficiency of the pancreas are rare side effects of ICI. In this review, we aim to elucidate different forms of ICI-related pancreatic involvement, their clinical relevance and potential strategies of their clinical management.

Lipase Elevation

Although lipase elevation is a common side effect of ICI, the medical significance remains uncertain. Recently, a multicentric study from the German Dermatooncology Group examined the relevance of lipase elevation and type I diabetes in melanoma patients treated with ICI [4]. In 68 patients with lipase elevation of at least >2.0 x upper limit normal (ULN) and a median of 6.4 x ULN, only 22% of the patients showed symptoms of pancreatitis, whereas 78% of the patients were asymptomatic. Patients with symptoms of pancreatitis showed a significantly higher extent of lipase increase (16.8 x ULN) compared to asymptomatic patients (7.8 x ULN) [4]. The occurrence of asymptomatic lipase elevation as an ICI-related adverse event in malignant melanoma has been reported previously. In a retrospective study of 119 melanoma patients treated with the combination of nivolumab and ipilimumab, Friedmann et al. described a 6.3% incidence of pancreatitis within 32 patients displaying a grade III or higher lipase elevation according to Common Terminology Criteria for Adverse Events (CTCAE) (>2 x ULN with symptoms or >5 x ULN without symptoms) [5]. Michot et al. presented a monocentric study of 909 patients receiving anti-PD-1 or anti-PD-L1 treatment regardless of treatment causality; 21 patients exhibited lipase increase at least >1.5 x ULN (CTCAE grade II) [6]. Of these 21 patients, only 14% were diagnosed with immune-related pancreatitis characterized either by abdominal pain or CT scan abnormalities, whereas 86% were asymptomatic [6]. Another monocentric study of 2279 patients receiving ICI for different malignancies showed a proportion of 4% with grade III - V lipase increase according to CTCAE [7]. In this cohort, 39% of the patients showed typical symptoms for pancreatitis, whereas 61% showed none of them. Further observations revealed that patients with clinical symptoms of pancreatitis developed higher mean peak levels of lipase than patients without symptoms [7].

Despite the broad evidence of pancreatic enzyme elevation in ICI treatment, the asymptomatic lipase increase as an isolated abnormal laboratory test and its causes remain poorly understood. Some authors suggest that elevated levels of lipase with no symptoms of pancreatitis and no radiological signs of pancreatitis are still based on pancreatic injury and should therefore be classified as type I pancreatic injury [8] or as an asymptomatic form of autoimmune pancreatitis type 3 [9]. As a proof for pancreatic injury during asymptomatic lipase increase, Thomas et al. reviewed serial pancreatic imaging of 93 patients receiving ICI treatment and found a loss of pancreatic volume associated with asymptomatic lipase elevation of ≥ 3 x ULN [9]. However, other authors suggest that lipase elevations could be nonspecific and caused by inflammation of nonpancreatic organs, for instance by inflammatory bowel disease, liver injury or renal impairment [4,5]. Even fluctuating lipase elevations in the absence of any pathologies have been described [10].

Clinical Management of Lipase Elevation

Current guidelines for the management of AEs in ICI treatment refer to pancreatic toxicity and the NCCN guideline state that treatment discontinuation is not usually recommended based on asymptomatic amylase and/or lipase elevation alone [11]. Nonetheless, whether to continue, to pause or to terminate ICI therapy or even to use corticosteroids in patients with lipase elevation is still a challenging decision faced by oncologists. Retrospective observations of a cohort of 68 patients with lipase elevation showed that in 35%, ICI was discontinued and led to a decrease of lipase levels to grade 0 or I according to CTCAE [4]. In 38% of the patients, ICI was interrupted and the same decline of lipase levels was noticed, however after reinduction of ICI, lipase increase recurred in 12 of 26 patients. The remaining 27% of the patients continued ICI treatment without changes despite lipase elevation and in 67% of these patients, lipase levels normalized in the follow up examinations [4]. This report indicates that continuation of ICI therapy can be considered upon lipase elevation and can even result in a decline of lipase levels. However, Friedman et al. point out that pausing immunotherapy and using steroids occasionally in case of asymptomatic lipase elevation cannot be excluded as therapeutic option to minimize subsequent pancreatitis [5]. Therefore, many authors suggest to temporarily interrupt ICI followed by reinduction once lipase values improve [6,7]. Nonetheless, clinicians should be aware of the discrepancy between lipase elevation and clinical pancreatitis and consider it in the decision about treatment continuation.

Routine measurement of lipase or amylase levels has recently been abandoned [4,5,8]. Since lipase elevation is often found in association with other irAEs [4,7], Abu-Sbeih et al. recommend to obtain lipase values in patients who are diagnosed with non-pancreatic irAEs [7]. However, given the low incidence of ICI-related pancreatitis the ASCO guideline states that routine monitoring of amylase or lipase in asymptomatic patients is not recommended and should only be initiated if a patient develops suggestive symptoms or suspicious radiologic findings for pancreatitis [12].

Acute Pancreatitis

Acute pancreatitis (AP) is a rare adverse event under ICI with an incidence around 2% in patients analyzed in clinical trials and real-world data [2,13]. It is more frequent in combined treatment with PD-1 antibodies and CTLA-4 antibodies compared to monotherapy [7]. Moreover, patients treated with ICI for melanoma were reported to have a higher frequency of AP compared to non-melanoma cancers [13]. Although pancreatic involvement is most commonly reported using the CTCAE, many authors prefer the revised Atlanta classification for diagnosis of AP [5,8,14]. According to the revised Atlanta classification, the diagnosis requires two of the following three features: (1) abdominal pain consistent

with acute pancreatitis, (2) serum lipase activity at least three times greater than the ULN and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography and less commonly magnetic resonance imaging or transabdominal ultrasonography [15]. The most common radiological signs in AP are segmental hypo-enhancement, stranding in the peripancreatic fat and pancreatic enlargement with heterogeneous delayed enhancement [7]. Even though AP may resolve, complications which need to be considered are pancreatic pseudocysts, chronic pancreatitis, pancreatic insufficiency or diabetes mellitus [16]. So far, no AP-related mortality has been reported [13].

Clinical Management of AP

When AP is diagnosed in a patient receiving ICI, other differential diagnoses including pancreatic metastases and pancreatic injury due to other causes (e.g. alcohol, hypertriglyceridemia, bile stones or sludge, autoimmune pancreatitis, pancreatic parenchyma neoplastic lesions, drugs other than ICI) should be excluded based on medical history, biochemical analyses, imaging and, if necessary, biopsies [16]. Further recommendations of the current ESMO guideline include withholding of ICI treatment in case of severe AP [16]. Continuing treatment throughout the pancreatitis, if symptomatically manageable, can be considered, especially since no mortality of ICI-related pancreatitis has been reported [13].

Treatment options for AP include intravenous (i.v.) hydration, pain control and corticosteroids. However, evidence on the reasonable application of these options is limited. Abu-Sbeih et al. observed that the use of steroids and i.v. fluids in ICI-related pancreatitis did not shorten the time to lipase value improvement, the duration of symptoms or the duration of hospitalization [7]. Several reports indicate that steroids are often used in patients with lipase elevation with or without symptoms of pancreatitis [4,5,8]. According to the ASCO guideline, the significance of corticosteroids in treating ICI-related pancreatitis is not clearly defined but they could be considered in symptomatic disease [12].

Diabetes Mellitus

Diabetes mellitus (DM), especially type I diabetes defined by an insufficiency of the pancreatic tissue to produce insulin, is a rather rare side effect of ICI. In a meta-analysis of 125 clinical trials involving patients treated with PD-1 and PD-L1 inhibitors, the incidence of type I diabetes was 0.43% with a high risk of a being a grade III or higher AE [17]. As often recognized, type I diabetes occurs more frequently in patients treated with a combination of PD-1 and CTLA-4 inhibitors compared to monotherapy [18] and is associated with other endocrine irAEs [4]. Clinically, increased liquid uptake and urine volumes often paired with nausea, abdominal pain and weight loss are reported by the patient and should raise awareness for the diagnosis of type I diabetes. In the laboratory work up, a glucose level above 126 mg/dl in fasting condition or 200 mg/dl in non-fasting condition is suggestive of the diagnosis [18]. The diagnosis of type I diabetes is not necessarily accompanied by an increase of the lipase level. In a multicentric study of melanoma patients, Grimmelmann et al. observed that 12 of 22 patients treated with ICI who developed type I diabetes displayed a lipase elevation [4]. The severe and life-threatening complication of type I diabetes, diabetic ketoacidosis, was significantly less frequent in patients with lipase elevation [4]. The differences in lipase elevation may reflect that type I diabetes can either be a consequence of pancreatic injury and pancreatitis or may be caused by other mechanisms. The pathogenesis of ICI-related diabetes is poorly understood so far. Although human pancreatic β cells are known to express PD-L1 and this expression has been shown to be upregulated in inflamed pancreatic islets and associated with $CD8^+$ T-cell infiltration [19], detailed mechanisms leading to pancreatic insufficiency need further exploration. Interestingly, compared to classic type I diabetes, the occurrence of islet autoantibodies is less frequent in ICI-related diabetes. In a recent review analyzing 90 cases of DM related to ICI with more than half of the patients treated for melanoma, only 53% were positive for at least one of the islet autoantibodies [20]. This reflects the possibility of different underlying mechanisms. Marchand et al. condensed different clinical courses of ICI-related diabetes into four types with potentially different pathophysiology including acute autoimmune insulin-dependent DM, type 2 diabetes-like phenotype, diabetes-induced by autoimmune pancreatitis, and diabetes following autoimmune lipoatrophy [21]. However, further and prospective investigation is needed to build a classification for different subtypes of ICI-related diabetes.

Clinical Management of DM

The importance of the awareness for diabetes as a rare ICI-related side effect is based on the potentially life-threatening course of the disease. The key is to detect and react to clinical signs and symptoms indicating the condition early on. In this context, the routine monitoring of blood glucose before each administration of ICI therapy is an important component and currently recommended by the ASCO and ESMO guidelines [12,16]. When DM is suspected, a laboratory workup including fasting blood glucose, glycated haemoglobin (HbA1c), anti-islet cell antibodies, anti-glutamic acid decarboxylase antibodies, urinary ketones, anion gap on a metabolic panel and C-peptide levels is recommended [12,16]. Furthermore, a consultation with an endocrinologist should be conducted because of the complex treatment regimen needed and the required patient education [12]. Hyperglycaemia with a low C-peptide or positive autoantibodies are suggestive for DM and can be managed with insulin replacement [16]. Hyperglycaemia with acidosis and ketosis indicates diabetic

ketoacidosis and needs to be treated with i.v. insulin, correction of fluid loss with i.v. fluids and close monitoring of serum potassium [16]. Although immunosuppressive treatment with corticosteroids is a standard treatment for most irAEs, high-dose corticosteroids have been unsuccessful in reversing ICI-related DM [22] and their application is not recommended [11,12,16].

Exocrine Pancreatic Insufficiency

In contrast to pancreatic endocrine insufficiency, pancreatic exocrine insufficiency (PEI) has been rarely described in literature [2,23-26]. It can present in the context of ICI-induced AP [2,23]. Only a few cases of isolated PEI following ICI have been reported [24,25]. Clinical symptoms include steatorrhea, irregular stools, abdominal pain and weight loss. In particular, diarrhea can be misdiagnosed for the common irAE colitis and the diagnosis of PEI should be excluded in each case [26]. The indirect test of fecal pancreatic elastase-1 is commonly used to diagnose moderate to severe PEI [27]. Whether steroid treatment should be used for management of ICI-related PEI is currently not clear. Recent guidelines on irAEs do not include recommendations on PEI treatment. In two reported cases, the patients were treated with steroids without any clinical response [24,25]. However, a substitution of enzymes by orally administered pancreatic enzymes capsules has been described to normalize the symptoms [2,23-26].

Conclusion

In this article, we have reviewed different forms of pancreatic involvement during ICI, ranging from lipase elevation to pancreatitis as well as endocrine and exocrine insufficiency of the pancreatic tissue. Asymptomatic lipase elevation is very often reported following treatment with CTLA-4-, PD-1- and PD-L1 antibodies. So far, only one of the current guidelines on management of irAEs states that discontinuation of ICI is not usually recommended based on asymptomatic lipase elevation alone [11]. Due to this inconclusive recommendation, the decision regarding treatment continuation remains difficult for many clinicians and further prospective investigations are needed, especially to evaluate the potential risk for pancreatitis after continuing treatment despite enhanced lipase levels. Other irAEs involving the pancreas are rare but should be kept in mind by clinicians due to their severe clinical course and, in case of diabetic ketoacidosis, potentially life-threatening outcome.

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