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Case Report: Pembrolizumab-Induced Epiglottitis in Early Triple Negative Breast Cancer

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1. Abstract

The neoadjuvant use of the immune check point inhibitor (ICI) pembrolizumab has significantly increased the complete pathological response (CPR) rate for early triple negative breast cancer (TNBC). However, pembrolizumab is associated with a variety of immune related adverse events (irAEs). Here we present a rare case of pembrolizumab-induced epiglottitis with mucositis. This case highlights the challenges of recognising and treating rare irAEs, where there is frequently a lack of published evidence to guide diagnosis and management. Severe irAEs can delay treatment and consequently affect patient outcomes, particularly in the curative setting. To our knowledge this is the first recorded case of pembrolizumab induced epiglottitis in a patient with TNBC.

1.2. Background

TNBC is associated with a higher risk of recurrence and poorer overall prognosis compared with other breast cancer subtypes [1]. ICIs have radically changed the standard of care (SOC) for TNBC following the landmark KEYNOTE-522 trial. The addition of pembrolizumab to SOC chemotherapy in the neoadjuvant and adjuvant setting was associated with a higher rate of CPR in patients with early-stage TNBC, and a significant improvement in overall survival [2,3]. Following neoadjuvant systemic treatment, the optimum time to surgery is four to eight weeks, which has been demonstrated to improve overall survival and disease-free progression [4].

Pembrolizumab is a monoclonal antibody which targets the T cell PD-1 receptor, facilitating immune recognition of cancer cells [5]. This immunomodulation is associated with a wide spectrum of irAEs which typically present as autoimmune-like or inflammatory conditions [6]. In early-stage TNBC treated with pembrolizumab 34% of patients experienced an irAE. 10.3% of patients experienced a grade 3/4 irAE [7]. Patients with a history of autoimmune disease are at an increased risk of developing irAEs [6].

Common irAEs include thyroiditis, hepatitis, pneumonitis, colitis, and cutaneous toxicities. These are well described with established diagnostic and management algorithms [8]. Rarer irAEs are less well defined, and consequently more difficult to diagnose and treat. A recent meta-analysis found that ICI-induced oral toxicities including mucositis, odynophagia and dysphagia occurred in less than 5% of patients and were generally low grade [9]. Resolution with topical treatment as well as systemic immunosuppression has been reported but there is a lack of evidence-based guidance to support investigation and management, particularly in steroid refractory cases [10]. Epiglottitis is a particularly rare irAE that can result in life threatening airway obstruction [11].

Here we report to our knowledge the first case of pembrolizumab induced epiglottitis in a patient with early TNBC. This case highlights the challenges of diagnosis and treatment of rare irAEs as well as the importance of early optimisation in the curative setting.

2. Case

A 49-year-old female was diagnosed with a 4x4 cm right breast malignant tumour and 3 suspicious ipsilateral axillary lymph nodes in January 2024. Breast core biopsy demonstrated a grade 2 invasive ductal carcinoma which was triple negative. A lymph node fine needle aspirate confirmed axillary nodal involvement. PET-CT ruled out distant metastases. While there was no definitive history of autoimmune disease, she was investigated for dermatomyositis, a rare auto-immune disease which classically presents as myopathy with characteristic skin changes. Family history included systemic lupus erythematosus but was otherwise unremarkable.

The patient commenced neoadjuvant SOC chemotherapy: four cycles of three-weekly carboplatin (at a dose based on an area under the concentration–time curve of 5 mg/ml/minute) with weekly paclitaxel (80 mg/m2) followed by four cycles of three-weekly epirubicin (90 mg/m2) with cyclophosphamide (600 mg/m2) (EC). Pembrolizumab (200mg, three-weekly) would ordinarily have started alongside chemotherapy from cycle one but was withheld pending specialist review concerning possible dermatomyositis. Case reports have highlighted a risk of ICI induced dermatomyositis flares in patients with a previous history of the disease [12,13]. Pembrolizumab was initiated from cycle 3. Treatment was uncomplicated with the exception of a single episode of febrile neutropenia following cycle 6, and EC was subsequently dose reduced to 80%. Neoadjuvant treatment was completed in July 2024. End of treatment MRI demonstrated an excellent partial response. She was subsequently planned for a right mastectomy and axillary node clearance (ANC) with a left mastectomy for symmetry in August 2024.

Four-weeks following the completion of neoadjuvant treatment, the patient presented to hospital with an eight-week history of gradually worsening odynophagia and severely reduced oral intake. She also reported episodes of food regurgitation streaked with blood. Three days previously she had attended the Emergency Department with the same symptoms and been discharged with omeprazole for suspected gastro-oesophageal reflux. On examination, her oral cavity appeared normal and flexible nasendoscopy (FNE) demonstrated no evidence of inflammation or ulceration. Blood tests including full blood count, liver function tests, urea & electrolytes, C-reactive protein and thyroid profile were unremarkable. An urgent outpatient oesophagogastroduodenoscopy (OGD) was scheduled.

She re-presented to hospital the following day with worsening odynophagia. Physical examination and CT head and neck were unremarkable. Immunotherapy-induced inflammation of the pharynx and larynx was considered a possible differential. Whilst awaiting an OGD, she commenced 1 mg/kg intravenous methylprednisolone (IV MTP), omeprazole 40mg twice daily (BD) and fluconazole to treat an irAE, oesophageal reflux and oropharyngeal candidiasis respectively. The OGD demonstrated multiple small, superficial ulcers along the greater curvature of the stomach and antrum, but no mucositis (Figure 1). Biopsy of these ulcers demonstrated mild reactive gastropathy. Further oesophageal biopsies were unremarkable. The patient improved symptomatically with IV MTP. However, in view of the gastric ulceration and diagnostic uncertainty of an irAE, IV MTP was stopped.

Due to the severity of her odynophagia, she remained an inpatient for IV hydration, nutritional optimisation, and further investigations ahead of her imminently planned mastectomy. She was unable to tolerate enteral feeding with a naso-gastric tube. An MRI of her head and neck indicated a mild degree of diffuse thickening of the mucosal surfaces in the superior hypopharynx, pharyngeal surface of the aryepiglottic folds, and the base of the lingual surface of the epiglottis suggestive of mucositis (Figure 2). A repeat FNE indicated mild inflammation of the mucosal surfaces at the tongue base, erythema of the epiglottis and normal laryngeal and vocal cord movements. IV MTP was re-started at 60 mg daily with the addition of oral soluble prednisolone (5mg QDS) to gargle and then ingest.

The patient's symptoms improved significantly with IV MTP. She underwent a mastectomy with ANC during the same admission. She required extensive support with IV hydration peri-operatively and additional pre-operative anaesthetic assessment due to the risk of laryngospasm secondary to epiglottitis. Histopathological review showed a CPR in the right breast and axilla. Seven days postoperatively, she was discharged on 60mg of prednisolone to be weaned by 10mg weekly. In view of the irAE and CPR, adjuvant pembrolizumab was withheld. She underwent adjuvant radiotherapy.

A repeat OGD four weeks later demonstrated mild non erosive antral gastritis with no ulceration. She was readmitted with odynophagia at a prednisolone dose of 10mg daily. An MRI of the head and neck showed prominent neck lymph nodes, which appeared reactive, but there was otherwise no evidence of recurrent mucosal thickening. FNE demonstrated inflammation of the posterior pharyngeal wall and secretions in keeping with mucositis. Steroid dose was re-escalated to IV MTP 40mg daily and infliximab 5 mg/kg was introduced as a secondary agent. In the following 24 hours the patient's symptoms improved, and she was discharged on 80 mg of prednisolone to be weaned by 5 mg every five days.

Infliximab was repeated at the same dose at two and six weeks. The patient reported symptomatic improvement for 1 week following the first two infliximab infusions, but no improvement following the third. A repeat FNE confirmed persistent mucositis, and she subsequently commenced MMF 1g BD while continuing a gradual wean of prednisolone. Clinical review at One and two weeks after commencing MMF showed significant symptomatic improvement.

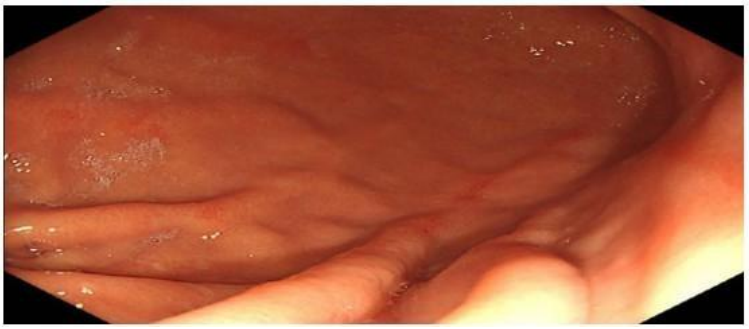

Figure 1: Oesophagogastroduodenoscopy showing small, superficial, linear ulcers in the greater curve of the stomach.

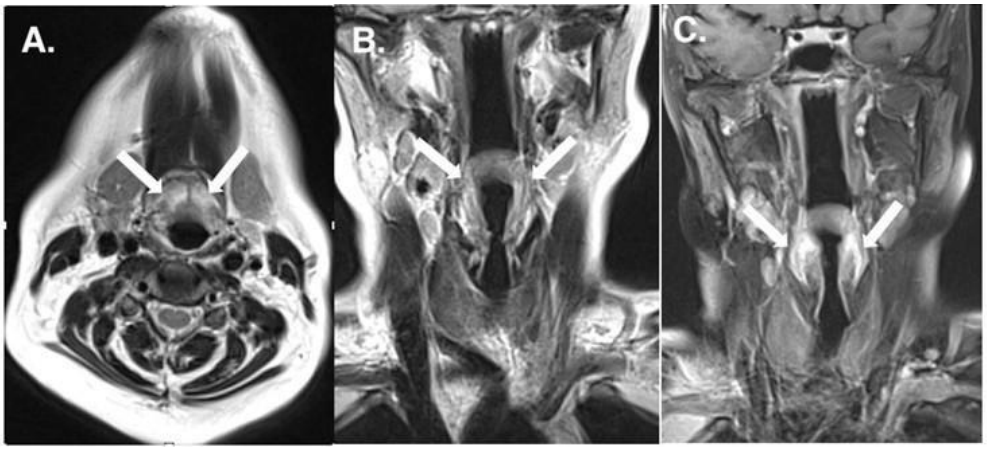

Figure 2 (A): Axial and (B) T2-weighted images show diffuse mucosal thickening at the pharyngeal surface of the aryepiglottic folds and at the base of the lingual surface of the epiglottis (white arrows). (C) Post-gadolinium T1 image shows enhancement in the mucosal thickening in the superior hypopharynx (white ar-rows). The appearance is suggestive of inflammatory mucosal thickening, such as mucositis/epiglottitis.

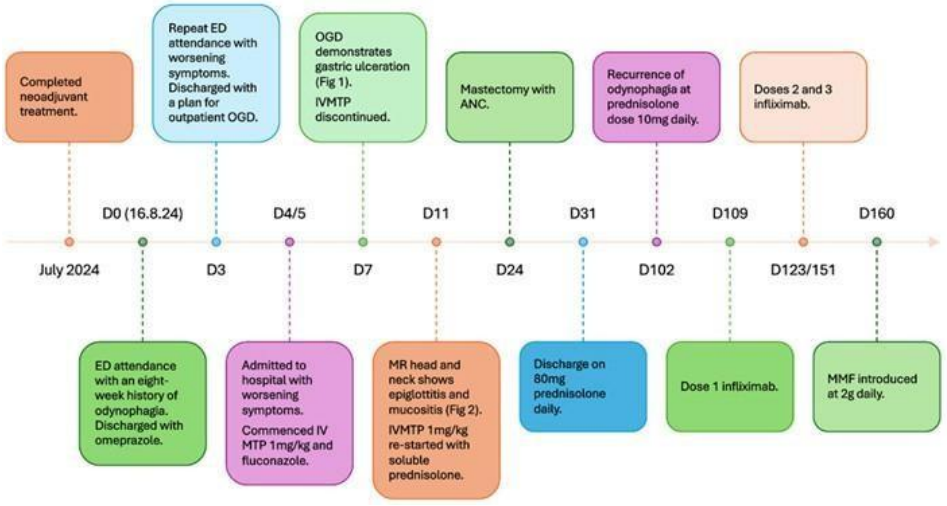

Figure 3: Timeline showing patient trajectory by day (D).

3. Discussion

To our knowledge, this is the first case in the literature to report epiglottitis secondary to neoadjuvant immunotherapy in early-stage TNBC. In the curative setting, prompt recognition and management of irAEs is particularly important to prevent treatment delays. Our patient presented with a diagnostic challenge. She was symptomatic with severe odynophagia, but initial investigations did not confirm an irAE or any obvious cause. Severe ICI induced mucositis is uncommon and consequently alternative diagnoses were extensively explored [9,10]. Despite negative initial investigations suspicion of an irAE remained high and further imaging and endoscopy confirmed this. This case underscores the importance of maintaining a high index of suspicion for irAEs in patient's presenting with atypical symptoms in the context of recent ICI treatment.

The KEYNOTE-522 study has shown that neoadjuvant pembrolizumab increases the proportion of Stage II and III TNBC patients achieving CPR [2,3]. There was no report of grade 3 mucositis or above after a median follow up of 75 months, or in published real world data on chemo-immunotherapy for early-stage TNBC [7]. Given its rarity, there is a lack of available guidelines to treat ICI-induced mucositis.

The patient's odynophagia improved with high dose steroids, but initial investigations did not provide evidence of macroscopic mucositis. The OGD findings demonstrating gastric ulceration posed a clinical dilemma due to the increased risk of perforation from steroid use. The steroids were initially paused and then re-started when MRI and repeat FNE confirmed the irAE. Unfortunately, her symptoms recurred on steroid weaning. Indeed, recurrence has been demonstrated in 39% of patients with ICI mucositis [10].

There is a lack of substantial evidence to guide the treatment of ICI mucositis in steroid refractory cases. We selected infliximab, a monoclonal antibody against anti TNF-alpha which is frequently used in immune-mediated colitis [14,15,16]. Infliximab was selected due to its rapid onset of action given the severity of the patient's odynophagia and risk of worsening epiglottitis. Infliximab alongside corticosteroids led to an initial rapid clinical benefit. However, this was short lived and only with the addition of MMF were we able to successfully treat this irAE. It is unclear why infliximab alone was unsuccessful and why the addition of MMF resulted in a sustained remission. The cellular drivers of ICI induced mucositis and epiglottitis are unknown. Further investigation of this would be helpful in establishing targeted strategies for the management of these rare irAEs.

4. Conclusion

The identification and treatment of irAEs is especially vital in the neoadjuvant setting to avoid delaying curative surgery. This case describes the diagnosis and management of pembrolizumab-induced epiglottitis with mucositis, a rare and challenging irAE. It emphasises the importance of considering irAEs in patients presenting with unusual symptoms such as odynophagia. Prompt diagnosis and management with IV MTP along with oral soluble prednisolone were key in optimising the patient pre-operatively.

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