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Therapeutic Challenges in Post-Transplant Lymphoproliferative Disorder of the Esophagus with Central Nerve System Involvement Complicated by an Esophagotracheal Fistula: A Case Report

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Keywords:

Post-transplant lymphoproliferative disorder; B-cell lymphoma; Tracheoesophageal fistula; Esophagus; CNS-Involvement.

1. Abstract

1.1 Background: Post-transplant lymphoproliferative disorder (PTLD) is a known complication following solid organ or hematopoietic stem cell transplantation. It's a heterogeneous group of lymphoid and/or plasmocytic proliferations as a result of immunosuppression and is frequently associated with Epstein-Barr Virus. The clinical presentation is nonspecific and highly variable depending on the localization. We discuss the therapeutic challenges in this rare case of a male suffering PTLD with esophageal involvement complicated by an esophagotracheal fistula.

1.2 Case Report: A 55-year-old man under immunosuppression after kidney transplantation, presented with progressive cough and fever after elective upper endoscopy. Following the diagnosis of diffuse large B cell lymphoma-type PTLD with esophagotracheal fistula. The reduction of immunosuppression was unable to control the progression of disease with involvement of the CNS. Endoscopic repair of the fistula was unsuccessful. The need for surgical repair of the fistula delayed therapy with rituximab by one month. Despite brain radiation therapy, the patient passed away 3.5 months after diagnosis.

1.3 Conclusion: In patients with esophagotracheal fistula both aspiration pneumonia and treatment of the fistula can delay effective treatment of the underlying malignant disease. In patients with PTLD reduction in immunosuppression is the primary treatment strategy, followed by monotherapy with the monoclonal antibody rituximab in the case of incomplete response. Newer therapeutic approaches prefer the sequential treatment with rituximab followed by chemotherapy in case of incomplete response, or consolidation therapy with rituximab in case of complete response. Radiotherapy is recommended in case of CNS involvement.

2. Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a known complication following solid organ or hematopoietic stem cell transplantation. It is a heterogeneous group of lymphoid and/or plasmocytic proliferations resulting from immunosuppression and it is frequently associated with Epstein-Barr virus (EBV). The 2017 WHO classification describes six subtypes of PTLD: classical Hodgkin lymphoma, monomorphic (B-, T-cell, or natural killer-cell types), polymorphic, florid follicular hyperplasia, infectious mononucleosis, and plasmocytic hyperplasia PTLD. The most common manifestation of PTLD is non-Hodgkin lymphoma of B-cell origin.

The incidence of PTLD depends on patient age, the transplanted organ, type and dosage regimen of immunosuppressive drugs and recipient Epstein-Barr virus status. The highest incidence of PTLD is observed in children and in small-intestine transplants, followed by thoracic organ transplants. The clinical presentation is nonspecific and highly variable depending on the localization. Extra nodal presentation of PTLD is frequent. The Ann Arbor classification is used as for non-Hodgkin lymphomas and most patients present

with advanced stage (III or IV) at diagnosis [1 – 10].

We report the case of a male patient with PTLD involving the esophagus complicated by esophagotracheal fistula. We discuss the therapeutic challenges taking into account the most relevant recent studies. The patient granted informed consent for the analysis and publication of this report.

3. Case Report

A 55-year-old man underwent kidney transplantation for diabetic nephropathy 20 years prior to the current disease. He was under immunosuppression with azathioprine. The patient presented with productive cough of 5 days duration and progressive fever with chills. Nine days earlier the patient had elective upper endoscopy for dysphagia, which revealed thick, foul-smelling, whitish lining of the proximal esophagus. A biopsy showed diffuse large B-cell lymphoma-type PTLD. Medical history included type 1 diabetes mellitus, chronic obstructive pulmonary disease, coronary heart disease, peripheral arterial disease, eosinophilic esophagitis and osteopenia. The patient had an ECOG performance status grade 1.

Physical examination revealed normal vital signs except for fever up to 38.5 °C. The remainder of the physical examination was normal, except for white coated oral mucous membrane, foul-smelling breath and rhonchi over all lung fields. No enlarged lymph nodes were palpable. The complete blood count revealed normochromic, normocytic anemia (Hb 100 g/L) with leukocytosis (12.1 G/L, predominantly neutrophilia) and plasma C-reactive protein (CRP) of 150 mg/l. The SARS-CoV-2 PCR test was negative.

The CT scan demonstrated an 8 mm esophagotracheal fistula 3 centimeters above the carina as well as peribronchial infiltrates in both lower lobes and in the lingula, without signs of mediastinitis (Figure 1). Intravenous antibiotic and antifungal therapy were initiated, as well as antiviral therapy due to a cytomegalovirus reactivation during hospital stay. Because of the distal location, elimination of the fistula was technically challenging despite repeated attempts by esophagoscopy and bronchoscopy. Finally, an esophageal stent was inserted, followed by repair of the posterior tracheal wall using a pedicled myocutaneous latissimus dorsi flap and esophagectomy with distal blind closure and cervical esophagostomy. Histology showed transmural infiltration of esophagus and trachea with EBV-related diffuse large B cell lymphoma corresponding to post-transplant lymphoproliferative disease with type III EBV latency. The initial 18FDG-PET-CT demonstrated increased activity in the esophagus only. An MRI of the brain showed three ring-enhancing subcortical lesions (Figure 2a). This observation was consistent with a possible central nervous system (CNS) involvement, despite the absence of malignant cells in the cerebrospinal fluid. Toxoplasmosis, tuberculosis or cryptococcus were excluded.

Immediately after hospital admission immunosuppression was reduced to the lowest effective dose. After successful wound healing, treatment with four weekly doses of rituximab (375mg/m2) was initiated. Therapy was well tolerated, and the patient could be discharged to inpatient rehabilitation.

Three weeks into rehabilitation, the patient was readmitted for severe hyperglycemia and progressive therapy-resistant headaches. The magnetic resonance imaging (MRI) showed multiple large-volume brain lesions (Figure 2b). Due to the significantly reduced general condition and high suspicion of lymphoma, we decided against biopsy and initiated whole-brain radiotherapy (10 x 3 Gy) which led to a gradual improvement of the general condition [11-25]. The patient was transferred to a nursing home for further care, where he died 3.5 months after diagnosis. Regrettably, no autopsy was performed.

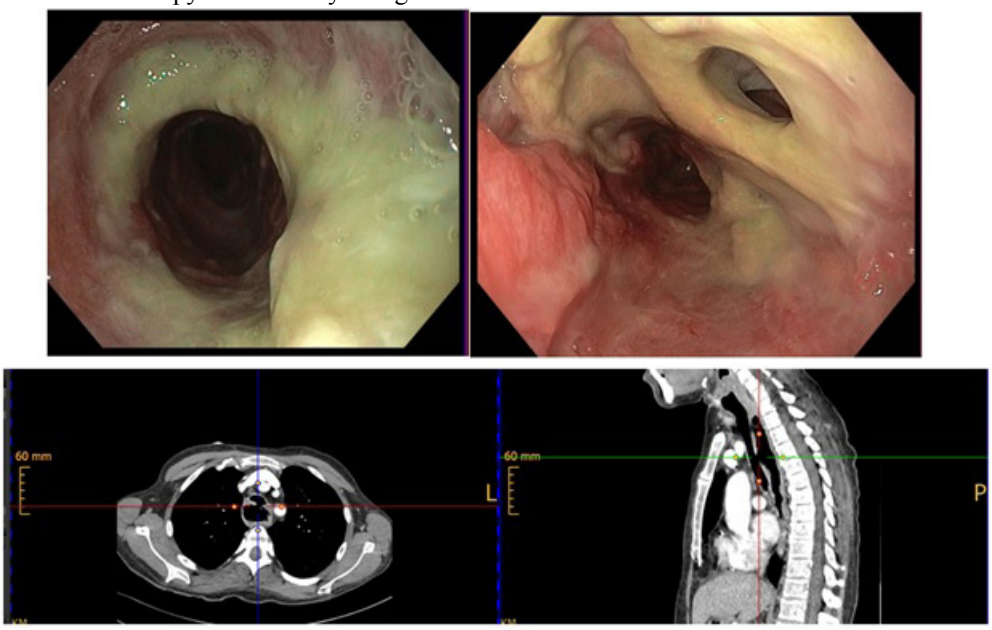

Figure 1a: Initial upper endoscopy before biopsy was performed. b. Computed tomography which showed the esophagotracheal fistula, 3 centimeters above the carina with a diameter of 7-9 millimeters. c. Esophagotracheal fistula seen in consecutive upper endoscopy.

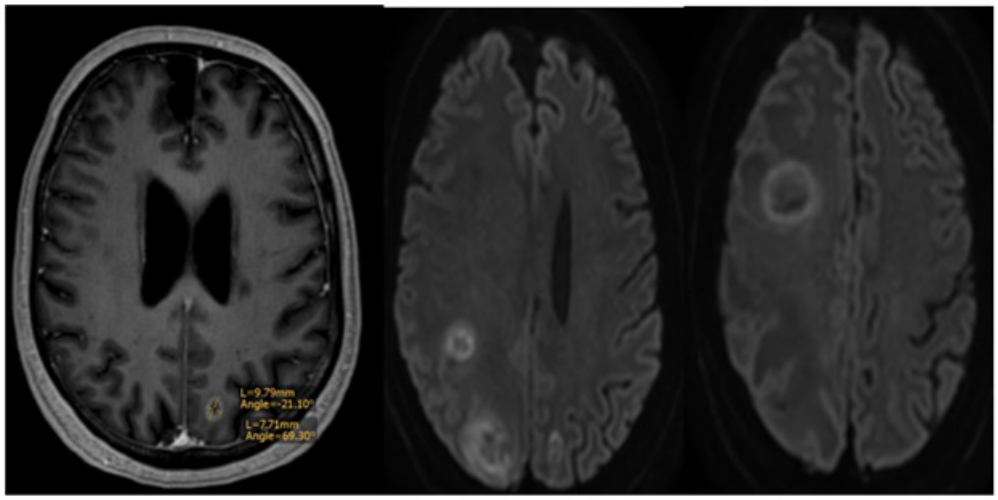

Figure 2a: The initial magnetic resonance imaging of the skull (T1 weighted), where three small ring enhancing lesions were found subcortically. b. Two months later the magnetic resonance imaging showed multiple large-volume brain tumors.

4. Discussion

In summary, we report a patient with PTLD involving the esophagus and the CNS following a renal transplant, in whom treatment was complicated and delayed by an esophagotracheal fistula after biopsy. So far, six cases with esophageal PTLD have been published, but no case was complicated by an esophagotracheal fistula. Only one case report was published describing a primary esophageal diffuse large B cell lymphoma presenting with esophagotracheal fistula, but this patient did not receive immunosuppression.

On average, 20 years after a renal transplant, 41 percent of the patients are alive and 62 percent of them have a functioning transplant. The 20 to 25-year incidence of PTLD following kidney transplantation is up to 3.5% for adults, with the incidence peaking in the first year and five to ten years after transplantation. Involvement of the intestinal tract occurs in 15 to 25% of patients, the stomach being most frequently affected.4, 8 Primary esophageal lymphoma is a rare disease, accounting for less than 1% of extranodal lymphomas. Involvement of the CNS is seen in 10-15% of patients with PTLD.4, Caillard et al. [1]. Reported a 5-year mortality of kidney transplant patients with PTLD of 53%. Independent indicators of poor survival were age over 55 years at diagnosis, CNS involvement and elevated creatinine levels as in our patient, as well as elevated serum lactate dehydrogenase levels, stage IV lymphoma, T-cell PTLD and monomorphic lymphoma.

The standard regimen of therapy for patients with diffuse large B cell lymphoma is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, in patients with PTLD of B-cell origin, reduction in immunosuppression is the primary treatment, with response rates ranging from 20 to 80%. Unfortunately, the reduction of immunosuppression leads to an acute rejection reaction in up to 37% of patients. If the reduction of immunosuppressants is not feasible or if no complete response is achieved after 3 to 4 weeks, monotherapy with rituximab (four weekly doses) is recommended for CD-20 positive PTLD. Chemotherapy with CHOP is used in relapse and in PTLD refractory to reduction of immunosuppression and rituximab. The use of chemotherapy was investigated in a cohort study by Trappe et al. [4]. Patients received rituximab followed by chemotherapy in case of incomplete response, or consolidation therapy with rituximab in case of complete response. Compared to a previous study with all patients receiving the same sequential treatment, this study showed lower rates of severe infections and treatment related mortality.

The esophagotracheal fistula was probably provoked by the biopsy in tumor tissue during the first gastroscopy. Because of the fistula, the patient then developed symptoms of aspiration pneumonia and presented on the emergency department. The incidence of iatrogenic upper gastrointestinal endoscopic perforation is low, occurring in 0.002% of the cases during diagnostic endoscopy. Other causes of an esophagotracheal fistula are malignant tumors, in particular esophageal or pulmonary malignancies treated with radiation or chemotherapy, or non-malignant, for example congenital or after endotracheal intubation. The main complication of esophagotracheal fistulas is tracheobronchial contamination and poor nutrition. Regarding treatment options, esophageal and tracheobronchial stenting is generally preferred over surgical treatment, but in selected patients tumor resection, exclusion and by-passing may be considered. For our patient repeated endoscopic intervention was unsuccessful, therefore surgical treatment was performed. This procedure delayed therapy with rituximab by one month. As staging showed involvement of the esophagus and possible CNS involvement, monotherapy with rituximab and reduction of immunosuppression was the preferred treatment protocol, primarily due to our patients' poor postoperative health status. The decision for the single-treatment regime with rituximab was based on the case report of Burnette et al. [22], where complete remission could be achieved in a patient with primary CNS lymphoma and contrain-

dications for chemotherapy. Because of the patient's significantly reduced general health status after esophagectomy with complete tumor resection and therapy with rituximab, sequential chemotherapy or consolidation therapy with rituximab was not feasible. Even though CNS involvement was very likely given the three ring enhancing brain lesions on initial MRI, whole brain irradiation was initiated only after confirmation of growth. The literature review by Izadi et al. [23]. Demonstrated significant improvement in one- and five-year survival using radiotherapy in PTLD with CNS involvement.

5. Conclusion and Outlook

Esophagotracheal fistula is a major treatment challenge and early elimination of the fistula is essential to prevent aspiration pneumonia. Both aspiration pneumonia and treatment of the fistula will delay effective treatment of the underlying malignant disease, requiring multidisciplinary approach to ensure timely initiation of specific cancer treatment. Thorough patient selection regarding relevant comorbidities and health status is crucial when selecting between the standard of care or a lesser aggressive and better tolerated cancer treatment strategy to optimize health gain for every single patient. Poor health and low physical reserves may require a lesser aggressive treatment, such as the one we have chosen for our patient.

The results of two studies concerning the treatment strategies are expected in about two years. The Research Group of Trappe et al. is currently investigating an updated stratification strategy and treatment adaptation for those at low- or very-high-risk. In Cleveland Clinic, the use of acalabrutinib, an inhibitor of Bruton Tyrosine Kinase, as addition to Rituximab is being investigated.

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