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Case report

Pulmonary embolism during the third cycle of alemtuzumab in a patient with relapsing multiple sclerosis

Mario Habek[a,b,*], Berislav Ruška[b], Tin Pavičić[b], Ana Marija Alduk[c], Tereza Gabelić[a,b], Ivan Adamec[b]

[a] School of Medicine, University of Zagreb, Zagreb, Croatia
[b] University Hospital Center Zagreb, Department of Neurology, Referral Center for Autonomic Nervous System Disorders, Zagreb, Croatia
[c] University Hospital Center Zagreb, Department of Radiology, Zagreb, Croatia

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ABSTRACT

Alemtuzumab is one of immunomodulatory drugs used for treatment of multiple sclerosis (MS). Although it is very effective it carries significant risk for various side effects. This paper reports a case of young patient who developed pulmonary embolism during the third cycle of alemtuzumab. It is suggested that awareness about possible vascular toxicity of this drug should be raised.

1. Introduction

Alemtuzumab is a humanized monoclonal antibody that causes depletion of the circulating B and T lymphocytes by targeting CD52 antigen expressed on the surface of these immune cells. The depletion that is profound and long lasting is very effective for treatment of the patients with highly active multiple sclerosis (MS) (Kalincik et al., 2017). However, its high effectiveness is offset by its safety profile with frequent side effects (Evan et al., 2018). Here we report a case of pulmonary embolism in a young patient, with highly active form of MS, as a possible serious adverse event associated with the third cycle of alemtuzumab treatment.

2. Case presentation

A female patient, with otherwise unremarkable medical history, was diagnosed with relapsing remitting multiple sclerosis (RRMS) in 2009 when she was 15 years old. The diagnosis was made only after a third time she developed neurological deficit, after which subcutaneous interferon beta 1a (IFN ß) was started. Due to significant side effects she experienced from IFN ß (headaches, flushing, injection site redness) she was switched to dimethyl fumarate in 2015. Follow-up MRI performed in January 2016 showed active brain and spinal cord lesions, some of which showed gadolinium enhancement. Two months after, in March 2016, she developed left optic neuritis with no significant improvement on corticosteroid treatment. Because of this relapse and MRI findings, which both indicated disease activity, it had been decided to switch disease modifying therapy (DMT) to alemtuzumab. After the second cycle of alemtuzumab which has been administered in 2017 she developed hypothyroidism for which she was started on levothyroxine.

Two follow-up MRIs over one year following the second alemtuzumab cycle showed active lesions, some with postcontrast enhancement. Additionally, the patient had another relapse in the form of right leg paresthesiae and vertigo. Therefore, it had been decided to administer third cycle of alemtuzumab. In December 2018, on the second day of the third cycle, after the first dose had been administered the day before, she started to complain about pressure in her lungs, shortness of breath and chest palpitations. Laboratory evaluation revealed elevated D-dimers (7.75 mg/l; normal value <0.50) and CT angiography of pulmonary artery showed filling defect of subsegmental lower lobe pulmonary artery representing pulmonary embolus (Fig. 1). Ultrasound of lower limbs showed no signs of DVT and tests for thrombophilia were negative. The patient received alemtuzumab in a an outpatient clinic and hypomobility was not considered as risk factor. Her body mass index was 20. Apart from levothyroxine, the patient wasn't taking any other medication. Administration of alemtuzumab was ceased and anticoagulant therapy was introduced in the form of low-molecular-weight heparin and rivaroxaban on which she fully recovered.

3. Discussion

Treatment with alemtuzumab, although highly effective in patients with MS, carries a significant risk of different side effects. Most significant side effects of alemtuzumab are infusion associated reactions,

* Corresponding author at: Department of Neurology, University Hospital Center Zagreb, Kišpatićeva 12, HR-10000 Zagreb, Croatia.
E-mail address: mhabek@mef.hr (M. Habek).

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Fig. 1. Axial pulmonary CT angiography image shows filling defect of subsegmental lower lobe pulmonary artery representing pulmonary embolus (arrow).

autoimmune disorders as well as opportunistic infections (Cohen et al., 2012).

The pulmonary embolism, from which the patient suffered after infusion of the third cycle of alemtuzumab, was previously reported as a possible side effect of this drug along with case of DVT in one clinical trial (Fox et al., 2012). However, it is also important to mention that other studies also report an increased risk of venous thromboembolism (VTE) in patients with MS in general (Ahmed et al., 2019). As stated by Ahmed et al., data that has been published is not clear whether the risk from VTE is increased because of risk factors such as hypomobility or drug treatment that are common in MS patients or is disease itself responsible for these events possibly by damaging vascular endothelium with inflammation (Ahmed et al., 2019).

Nevertheless, if we take into consideration the onset time of this event which is within one day of the infusion as well as the fact that patient, apart from MS, had no other risk factors for (such as hypomobility or treatment with DVT risk increasing drugs) or signs of trombophilia, it is very reasonable to speculate that embolism was a direct consequence of the alemtuzumab infusion. Furthermore, in November 2018, The US Food and Drug Administration (FDA) issued a warning about cases of stroke and tears in the lining of arteries in the head and neck that have occurred in patients with multiple sclerosis shortly after they received alemtuzumab. Additionally, there was one case of thrombotic microangiopathy in patient treated with this drug (Liou et al., 2018). Above mentioned cases are consistent with our case thus suggesting possible vascular toxicity of alemtuzumab that has not been widely recognized in previous clinical trials and that awareness about this toxicity should be raised among clinicians.

Adverse event report

This adverse event has been reported to The Croatian Agency for Medicinal Products and Medical Devices.

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Mario Habek: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Writing - review & editing. **Berislav Ruška:** Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Tin Pavičić:** Data curation, Formal analysis, Writing - review & editing. **Ana Marija Alduk:** Data curation, Formal analysis, Funding acquisition, Writing - review & editing. **Tereza Gabelić:** Data curation, Formal analysis, Funding acquisition, Writing - review & editing. **Ivan Adamec:** Data curation, Formal analysis, Funding acquisition, Writing - review & editing.

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