Severe herpes simplex oral mucositis in a patient with non-Hodgkin’s lymphoma after autologous stem cells transplantation – Case Report

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Abstract

The study presents the case of a 25-year-old patient with the diagnosis of diffuse large B cell lymphoma treated autologously with haematopoietic stem cells transplantation. During the period of aplasia after chemotherapy severe sore lips, mouth and esophagus herpes simplex mucositis developed and is successfully treated with foscarnet. The clinical course, localized causal and symptomatic treatment, along with the therapy imaging, are presented.

Key words

herpes simplex mucositis, non-Hodgkin’s lymphoma, autologous haematopoietic stem cells transplantation, foscarnet

INTRODUCTION

Mucositis is inflammation of the mucous membrane, known as mucosal barrier injury (MBI), which can be located within the oral cavity – oral MBI (OMBI), or further sections of the gastrointestinal tract – gut MBI (GMBI). Mucositis occurs in approximately 76–89% of patients with haematological malignancies treated with intensive chemotherapy, including conditioning myeloablative therapy prior to autologous haematopoietic stem cell transplantation (auto-HSCT). The occurrence of MBI depends on many factors: the protocol used in chemotherapy, radiotherapy, completed and concomitant diseases, age, gender, health and oral microflora, salivary gland function, or addictions. Pathological processes occurring in the course of MBI may be benign inflammatory lesions, erosions, or difficult-to-heal ulcers, which has a significant impact on the quality of the patient’s life. Furthermore, due to violation of natural mucosal barrier by breaking the continuity of tissues and impairment of host defence processes, MBI favours the occurrence of secondary infections – viral, fungal and bacterial, which can be severe and life-threatening.

Clinically, changes in the course of oral mucositis are frequently classified according to the Oral Toxicity Scale (OTS) developed by the World Health Organization (WHO). The WHO scale takes into account an assessment of anatomical changes, clinical symptoms and functional disorders in the course of mucositis, in 5 grades of severity. According to OTS, grade 0 – no lesions, 1 – erythema ± pain, 2 – erythema, ulceration, the patient can take solid foods, 3 – ulcers, with massive oedema, the patient is unable to eat solid foods, 4 – advanced mucositis prevents the intake of any food.

The cytostatics having a particularly toxic effect on the mucous membrane and responsible for the occurrence of MBI include: folic acid antagonists (methotrexate), anthraclycine (idarubicin, daunorubicin, doxorubicin), pyrimidine analogs (5-fluouracil, cytosine arabinoside), alkylating agents (high dose melphalan, busulfan, cyclophosphamide), cisplatin and carboplatin, topoisomerase II inhibitors (etoposide, irinotecan), and purine analogues (fludarabine, cladribine). Most of these drugs reach the mucosa via blood vessels. Methotrexate, and etoposide are also secreted into the saliva and can therefore directly damage the mucosa. Damage to the protective barrier of the oral mucosa by cytotoxic agents results in its high susceptibility to the very diverse microbiotic oral environment, including gram-positive, gram-negative bacteria, fungi, in particular from the group of Candida, viruses, as well as exogenous microorganisms. Viral infections, being a complication of myeloblastic therapy, are very serious problem for both health and the economy. Their effects include a severe course of inflammation of the mucous membranes with massive ulcers, severe pain preventing the intake of food and liquids, requiring parenteral nutrition, analgesic treatment and contribute to longer hospitalization and increased costs of treatment.

Herpes simplex virus -1 (HSV-1) is present within the oral mucosa and, together with other viral pathogens (Epstein-Barr virus, EBV, cytomegalovirus, CMV), may be an important pathognomonic factor in the development of OMI. Herpes viruses are characterized by high resistance to antiviral treatment and are an important negative factor in the etiology and course of OMI.

Clinically, infection with HSV-1 can manifest itself in the form of severe mucositis, inflammation of the lungs or gastrointestinal tract [1]. Primary infection with HSV-1 usually occurs in childhood and exists in a latent form in the trigeminal ganglia. In adults, the factors causing reactivation of viral replication include: sunlight, stress, trauma, fever, immunosuppression. Each replication process manifests itself in the form of recurrent infection with herpes labialis, or sometimes erosions in the mouth. In the case of herpes labialis, usually the first symptom of changes occurring on
the mucocutaneous border is itching, burning, tingling, or pain. Clinically, herpetic lesions are manifested in the form of a spot, then a lump on the base, wherein within 48 hours numerous vesicles are formed. After 72–96 h, changes take the form of pustules, crusts, which heal without scarring. In the mouth, erosions may occur locating the hard palate or gums that disappear after 1–2 weeks. In the case of immuno-suppressed patients, changes initially take the form of proliferating erosion-ulcerative changes, and besides the typical location, they are often also on the dorsal side of the tongue [2].

CASE REPORT

A 25-year old male patient diagnosed with diffuse large B-cell lymphoma (DLBCL), an originally resistant form of the disease, after 3 lines of chemotherapy and radiotherapy of neck, was qualified to high dose chemotherapy procedure supported with autologous hematopoietic stem cell transplantation. In the conditioning, R-BEAM protocol was used (rituximab, BiCNU, etoposide, cytosine arabinoside, melphalan) in maximum doses because of the high activity of the disease and resistance to current treatment. Acyclovir was used in the prophylaxis of viral infections.

In the dental examination before the conditioning procedure, there were no pathological lesions on the mucosa of the lips, cheeks, hard and soft palate, floor of the mouth; only the tongue ridge was covered with a thin, clear coating (2nd degree Winkle tongue coating), and the gum showed a slight state of inflammation manifested by bleeding on probing (gingival sulcus bleeding index [GSBI], 1st degree). Clinical examination and evaluation of the orthopantomographic images did not reveal the presence of dead teeth, nor endodontically treated teeth. For the assessment of oral hygiene, Oral Hygiene Index (OHI) by Greene and Vermillion was used, whose average for the dental calculus was 0 and for plaque – 1. In the extraoral examination, there were no pathological changes on upper and lower vermilion borders.

During prolonged marrow aplasia after chemotherapy, inflammation of the oral mucosa, lips, throat and oesophagus of a mucositis type was observed. Grade 4 of mucositis was diagnosed according to the WHO grading scale, requiring administration of narcotic analgesics and application of parenteral nutrition for a period of 38 days. Diagnosis of severe MBI revealed the presence of HSV-1 in blood by PCR test; viral infections CMV and EBV were excluded.

Infection with HSV-1 proceeded with simultaneous, deep bone marrow suppression and prolonging recovery of all cell lines. This resulted in the need to use a number of transfusions of red blood cell concentrates (16 units) and platelet concentrates (16 packs).

The patient required the use of broad-spectrum antibiotics therapy, antifungal agents (fluconazole, caspofungin) and
intravenous immunoglobulin preparations. In the treatment of herpetic mucositis, due to marrow aplasia, foscarnet was applied, instead of the reference acyclovir. Improvement of the general condition of the patient, together with the healing of erosions and ulcerative chan ges, was observed after 7 days of treatment with foscarnet. At the same time, normal bone marrow regeneration with improved blood counts were observed and resignation of the need for transfusion of blood products. The patient was discharged from hospital on day 44 after bone marrow transplantation. The healing period of lesions in the oral cavity after discharge from the hospital was another 28 days, but it allowed for liquid alimentation.

This patient with the WHO Grade 4 mucositis was unable to open his mouth, which rendered clinical evaluation of lesions in the oral cavity considerably difficult. Inflammatory lesions in the course of infection with HSV-1 also affected almost the entire surface of the lower vermilion border. They took the form of bleeding erosions and ulcers, which had a tendency to proliferate, forming large scabs. Transformation of inflammatory lesions in the patient proceeded without follicular and vesicular phases. During hospitalization, advanced mucosal inflammation and pain in the oral cavity (assessed by the patient at the level of 6–8 in a 10-point visual-analog scale of subjective assessment of pain) limited the implementation of full hygienisation of the oral cavity. The patient was not able to brush his teeth. Only on day 14 after auto-transplantation, a lotion containing a mixture of drugs: benzocaine, neomycin, hydrocortisone and nystatin, could be introduced, as well as the use of Corsodyl and Fungizone, followed by Caphosol.

DISCUSSION

Viral infections of the oral mucosa are a serious complication of chemotherapy and radiotherapy in patients with haematologic malignancies [3, 4]. Herpes simplex viruses are detected in 58–70% of haematology patients treated with intensive chemotherapy [5]. The response of HSV-1 is activated specifically in the 3rd and 4th grade of OMI severity, with concomitant neutropenia, leading to formation of endothelial vesicles that rupture, releasing exudate, comprising among others, fibrin forming pseudo-membranes, which makes the course of OMI extremely aggressive and resistant to treatment. Chen et al. reported that antifungal drugs could be introduced, as well as the use of Corsodyl and Fungizone, however, does not guarantee the absence of complications of a mucositis type. In the case of severe course of the oral mucositis type, one should keep in mind that the reason, among others, May be coexisting HSV-1 infection. In some cases, patients eligible for bone marrow transplantation should have marked concentration of HSV antibodies, the IgG type, before starting the procedure despite the fact that such a procedure is not standard. Furthermore, the presence of new strains of HSV-1 resistant to acyclovir treatment remains a major therapeutic problem.

CONCLUSION

It is extremely important to prepare the patient for bone marrow graft, not only from the general-medical, but also dental point of view, involving the sanation and hygienisation of the mouth. Caring for these elements, as well as compliance with the regime of transplantation procedure, the use of antiviral, antibacterial, antifungal prophylaxis, however, does not guarantee the absence of complications of a mucositis type. In the case of severe course of the oral mucositis type, one should keep in mind that the reason, among others, May be coexisting HSV-1 infection. In some cases, patients eligible for bone marrow transplantation should have marked concentration of HSV antibodies, the IgG type, before starting the procedure despite the fact that such a procedure is not standard. Furthermore, the presence of new strains of HSV-1 resistant to acyclovir treatment remains a major therapeutic problem.

In the described case, herpes mucositis in a patient led to extensive ulcerative changes requiring long-term parenteral nutrition, use of narcotic analgesics, anti-infectives and significantly prolonged bone marrow recovery time, hospital stay, and thus increased the cost of treatment.
REFERENCES