Oral lesions in paediatric patients with graft-versus-host disease

INTRODUCTION

In paediatrics, the use of haematopoietic stem cell transplantation techniques has recently been extended to neoplastic patients and patients affected by non neoplastic haematological diseases, such as primary immunodeficiency, aplastic anaemia, sickle cell anaemia and thalassemia [Fonseca, 2008].

Haematopoietic stem cell transplantation is therefore more and more common in paediatric patients since it can offer a possibility of cure and long-term survival. However, under specific physiopathological conditions, it seems to be the main cause of the onset of a particularly debilitating syndrome: the Graft-versus-Host Disease (GvHD) [Ferrara, 1991; Ferrara, 1997]. GvHD is therefore the main complication, and cause of morbidity and mortality in haematopoietic stem cell transplantation recipients [Jacobsohn, 2002; Parkman, 1998].

GvHD is characterised by specific pathological and immunological manifestations, due to the transplantation of immunologically active T lymphocytes of a donor with a genome different from the recipient’s into a compromised immune system [Ferrara, 1991; Ferrara, 1997].

Even though GvHD is deemed an undesirable complication, it produces an important beneficial effect on the body, as it has recently been proved that the donor’s T lymphocytes not only massively attack the receiving’s healthy cells and tissue, but also spot and suppress cancerous cells, thus contributing to the remission of the disease [Mookerjee, 1999; Flowers, 2002].

The complex physiopathology of this syndrome is still unknown, however, a number of scientific research works seem to demonstrate a strong relationship between it and an increased production of y interferon and cytokines IL-4 and IL6 [Mookerjee, 1999; Franca, 2001]. At present, GvHD is clinically classified into the two following forms, rather than according to the time of onset (before or after 100 days): acute (aGvHD) if produced only by the cytotoxic effects of the donor’s T lymphocytes at the host tissue level, in particular epithelial cells, and chronic (cGvHD), when it is caused by a cytotoxic effect associated with severe immunodeficiency due to an alteration in the production and function of the host’s T and B lymphocytes [Flowers, 2002; Laughlin, 2004]. Both forms can last months or even years and require specific long-term multidisciplinary clinical monitoring protocols [Parkman, 1998].

Even if most of GvHD symptoms are skin-related, over 90% of affected patients also progressively and significantly develop an involvement of the oral mucosa [Nicolatou-Galitis, 2001].

In this work, the authors intend to evaluate and describe the most frequent clinical manifestations of the Graft-versus-Host Disease (GvHD) in the oral and maxillofacial region in paediatric patients affected by neoplastic or non neoplastic haematologic disorders who undergo specific haematopoietic stem cell transplantation (HSCT) protocols, with a view to detecting the potential pathological modifications that are recognised as the cause of a possible altered harmonious development of the child.

MATERIALS AND METHODS

Thirty-eight paediatric patients aged between 3 and 13 years, coming from the haematological department of Tor Vergata University (Roma, Italy) and affected by GvHD, assessed on the basis of their medical history and accurate clinical and instrumental exams, after having received haematopoietic stem cell transplantation for neoplastic or non neoplastic haematologic disorders, were enrolled in this study. The aim of this work was to assess oral conditions, detect possible oral pathological manifestations and evaluate their incidence both locally and in terms of clinical severity, as well as to mitigate associated symptoms. This was done to prevent and eliminate any oral interference in the systemic treatment protocol.

DISCUSSION AND CONCLUSION

In line with the data presented in the literature, clinical GvHD manifestations seem to mainly involve the oral and maxillofacial region from an early phase also in paediatric patients. As a consequence, a timely diagnosis and a multidisciplinary treatment programme are essential for the early detection of the oral signs of potential systemic complications, to improve the quality of life of these young patients, as well as to prevent any potential alterations of dentoskeletal development and growth in the child.

Keywords: GvHD; Oral manifestations; Paediatric patients.

Materials and methods

From November 2006 to December 2008, a total of 38 paediatric patients aged between 3 and 13 years (mean age 8.9; 22 male and 16 female), coming from the haematological department of Tor Vergata University (Roma, Italy) with a diagnosis of GvHD, in a period...
between 90 and 180 days after having received haematopoietic stem cell transplantation for neoplastic or non neoplastic haematological disorders, were visited at the Paediatric Outpatient Clinic of Dental Surgery of the Tor Vergata Hospital. The assessment was performed on the basis of their medical history in order to timely assess oral conditions, detect any pathological manifestations, and evaluate their incidence both locally and in terms of clinical severity to mitigate symptoms, with a view to preventing and eliminating any oral interference to the systemic treatment protocol needed following the bone marrow transplantation programme.

Each patient underwent intra- and extra-oral clinical evaluations.

At the extraoral examination, 10 patients (26% of the cohort) showed sparse, thin and frail hair, eye dryness and visible lichenoid and sclerodermic alterations of the facial skin around the eyes, nose, mouth and chin (Fig. 1, 2). These lesions appear in the form of hypopigmented or hyperpigmented, sclerotic and scarcely hydrated areas characterised by peeling scales of epithelial cells accompanied by diffuse erythema (Fig. 3).

At the intraoral examination, patients opened the mouth slightly and with difficulty. This was due both to mucosal sclerosis and the face epithelium, and to the limited mobility of the soft tissue of the lip and tongue caused by fibrosis, which revealed the serious involvement of the stomatognathic apparatus (Fig. 4, 5).

Seventeen subjects (45% of the cohort) showed clinical signs and symptoms of oral GvHD: debilitating dysphagia, general oral alagic sensation mainly due to unspecified odontalgia, dryness and burning of oral mucosa, glossopathy and altered perception of the taste of spicy food and/or acid drinks.

Clinical reports on the oral cavity revealed the following: 31% of the patients showed erosive lesions of the enamel, white spots, invasive tooth decay, radicular residues of deciduous teeth; 42% showed aphthosis ulcerations, vesicular eruptions similar to herpetic lesions and lichenoid reactions on the tongue and cheek mucosa with white striae producing uniform plaques localised within huge hyperpigmented purple areas (Fig. 6, 7, 8).

Moreover, in 39% of the cases the oral mucosa appeared depigmented, dry, pale and atrophic and characterised by erosive plaques and ulcerative lesions on the adjacent gum
Aspecific, superficial lesions were found on the mucosa adhering to the palate (26% of the cases), while the tongue was affected in 34% of the subjects by a form of atrophic glossitis characterised by the presence of smooth, depapillated and confluent areas, similar to small islands outlined by a huge ulcerative lesion located on the ventral portion of the dorsum linguae.

The involvement of salivary glands was observed in 34% of subjects by a significantly reduced salivary flow, general dryness, and pale and atrophic mucosa.

The clinical picture was further aggravated by the persistence of severe xerostomia which made any therapeutic activity, even a simple clinical inspection, difficult and painful [Nagler, 1996].

General mucosal lesions were observed in all of the 17 patients with oral GvHD. In fact, in these patients, the oral mucosa shows a significant level of atrophy and severe erythema; ulcerations exclusively localised on the non keratinised mucosa were observed on the oral floor, cheek, lip and tongue mucosa.

**Discussion**

GvHD is one of the most important complications following bone marrow transplantation, as it affects target organs, such as skin, liver, gastrointestinal tract, oral mucosa and salivary glands. In particular, the oral form of GvHD is present in 80-90% of systemic GvHD patients [Maiguma, 2008].

Even if in the literature oral adult GvHD has been thoroughly studied both clinically and scientifically, the description of this syndrome in paediatric patients is rather limited, despite the high incidence in this population group [Jacobsohn, 2004].
Some authors state that the clinical incidence of cGvHD after HSTC may vary from 13% to 80%; in particular, 13% of patients aged below 10, 28% of patients between 10 and 19 years of age, and over 40% in individuals over 20 [Imanguli, 2008].

The incidence of oral cGvHD manifestations in paediatric patients amounts to 45% [Jacobsohn, 2002].

In most cases, oral lesions represent the first or even the only manifestation of GvHD [Mai guma, 2008; Mattson, 1992]. The chronic form of the syndrome has a significant impact on morbidity and quality of life, because oral manifestations imply more severe and long-term complications, as opposed to the typical acute form, even if both may interfere with the bone development and growth of the individual.

Literature agrees on the fact that ectodermic lesions, such as the pathological alterations of hair, nails, skin and mucosa represent the early and most frequent clinical alterations of GvHD [Andrews, 1997; Itin, 1996].

The lesions affecting oral tissues, such as atrophy, erythema, ulcers, mucositis and lichenoid lesions, are accompanied by recurrent phenomena of dysgeusia, xerostomia, trismus, and hypofunctioning salivary glands and seem to reproduce certain autoimmune diseases (lichen planus, lupus erythematous, scleroderma and Sjögren's syndrome), in fact, GvHD is more and more frequently associated with oral pathologies of precancerous and even malignant nature [Mattson, 1992; Parkman, 1998]. A number of authors believe that erythematous, reticular and ulcerative forms of the oral mucosa lesions are indicative of the dynamic nature of this pathological condition in children [Jacobsohn, 2007; Palencia, 2002].

Unlike aGvHD, that shows clinical manifestations 2-3 weeks after transplantation, such as erythema, erosion and ulceration of oral mucosa, the pathological modifications produced by cGvHD, can only be recognised 70 days following transplantation [Franca, 2001]. These forms are clinically similar to acute forms, but are accompanied by typical white protruding plaques, and red striae similar to those found in lichen planus and, as a consequence, they are characterised by sclerotic mucosal variations and a reticular, erythematous or ulcerative involvement [Aractingi, 1996; Demarosi, 2007]. Finally, the persistent reduction of salivary function causes oral disorders: reduced mobility of the mouth, sensibility or pain when eating spices, alcohol or food containing flavouring agents, greater incidence of tooth decay, and ulcers, mucositis and lichenoid reactions) induced by GvHD, and specific oral hystopathological lesions (atrophy, erythema, lichenoid reactions) induced by GvHD, and specific oral manifestations associated with lesions of the face, hands, gastric mucosa, as well as a general aspecific oral alga. It is however evident that the functional impact of GvHD oral lesions is so significant that the general picture of disorders associated with pain prevents patients from appropriately eating, thus forcing them to reduce food intake, and subsequent underweight or suboptimal bone growth and development [Eggleston, 1998; Naggler, 1999].

Even if the presence of oral lesions alone does not allow acute forms to be told from chronic ones, several studies have shown that the development of oral lichenoid lesions is related to cGvHD in statistically significant terms [Barret,1984; Mookerjee, 1999; Nakamura, 1996].

Conclusion

Paediatric patients affected by neoplastic and non neoplastic haematological disorders that undergo HSCT protocols often develop oral lesions, some of which are so severe that they interfere with normal swallowing, feeding and talking activities [Nakhleh, 1989; Itin, 1996].

Even if in the past few years scientific research has optimised techniques and procedures of haematopoietic stem cell transplantation and proposed improvements to protocols in order to prevent the development of long-term complications, GvHD still is the most severe and recurrent complication in about 20-50% of HSCT patients [Aschan, 1994; Easaw, 1996]. For this reason, a role of primary importance is played by an early oral diagnosis, because the timely detection of the initial phase of this complex and dynamic syndrome in paediatric patients means to recognise the early signs and symptoms of a rapidly evolving systemic condition, which can have a serious influence on the prognosis and future quality of life of these subjects [Mookerjee, 1999; Andrews, 1997].

References

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