case report

ORAL MANIFESTATIONS IN THE GRAFT VERSUS HOST DISEASE IN PAEDIATRIC PATIENTS: CASE REPORT

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SUMMARY

Oral manifestations in the Graft versus Host Disease in paediatric patients: case report

Graft-versus-Host Disease (GvHD) syndrome is characterized by specific pathologic and immunologic clinical manifestations, induced by the transplantation, in a body with compromised immune system, of immunologically active T lymphocytes belonging to a donor whose genome is different from the recipient. GvHD can be clinically classified into two forms: acute (aGvHD), if it is induced only by the cytotoxic effect of the donor T lymphocytes in host tissues and chronic (cGvHD), when it is caused by a cytotoxic effect associated with severe immunodeficiency.

Patients affected by GvHD frequently develop a massive and progressive involvement of the oral mucosa, being so severe to impair normal feeding as well.

The Authors hereby introduce a GvHD clinical case in a 12-year-old patient who underwent Hematopoietic Stem Cell Transplantation (HSCT) from a compatible donor, with odonto-stomatological diseases induced by the syndrome. Early diagnosis and a multidisciplinary treatment plan in the initial phases of this complex and dynamic syndrome are key factors to improve the quality of life in these patients.

Key words: oral manifestations, GvHD, paediatric patient.

RIASSUNTO

Manifestazioni orali della Graft versus Host Disease nel paziente pediatrico: caso clinico

La *Graft-versus-Host Disease* (GvHD) è una sindrome caratterizzata da specifiche manifestazioni cliniche patologiche e immunologiche, derivanti dal trapianto in un organismo con sistema immunitario compromesso, di linfociti-T immunologicamente attivi appartenenti ad un donatore con un genoma diverso da quello del ricevente. La GvHD è classificata su base clinica in due forme: acuta (aGvHD), se indotta dal solo effetto citotossico dei linfociti-T del donatore a livello dei tessuti dell'ospite, e cronica (cGvHD), quando causata da un effetto citotossico al quale si associa una grave immunodeficienza.

I pazienti affetti da GvHD frequentemente sviluppano un imponente e progressivo coinvolgimento della mucosa orale, talmente grave da interferire anche con la normale alimentazione.

Gli Autori presentano un caso clinico di GvHD in un paziente di 12 anni sottoposto al trapianto di cellule staminali emopoietiche (HSCT, *Hematopoietic Stem Cell Transplantation*) da donatore compatibile, che presentava patologie odontostomatologiche riconducibili a tale sindrome. Una diagnosi tempestiva e un piano di trattamento multidisciplinare, nelle fasi iniziali di tale complessa e dinamica sindrome, sono essenziali per migliorare la qualità di vita di questi pazienti.

Parole chiave: manifestazioni orali, GvHD, paziente pediatrico.

Introduction

In paediatrics, the use of Hematopoietic Stem Cell Transplantation techniques has been recently extended to neoplastic patients and patients affected by nonneoplastic hematologic diseases such as primary immunodeficiency, aplastic anemia and thalassaemia (1, 2).

Although Hematopoietic Stem Cell Transplantation (HSCT) can offer a long-term survival therapeutic chance, it has been demonstrated that, in

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specific physiopathological conditions, HTSC stands for the primary cause in the onset of a specific debilitating disorder: the Graft-versus-Host Disease (GvHD). This disease currently accounts for the leading disorder and cause for morbidity and mortality in the allogenic stem cell transplant (3, 4).

Graft-versus-Host Disease (GvHD) syndrome is characterized by specific pathologic and immunologic clinical manifestations, induced by the transplantation, in a body with compromised immune system, of immunologically active T lymphocytes belonging to a donor whose genome is different from the host one (5, 6). GvHD can be clinically classified into two forms: acute (aGvHD), if it is induced only by the cytotoxic effect of the donor T lymphocytes in host tissues, in particular on 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 T and B host lymphocytes. Both forms can last for months or years and require, anyway, specific multidisciplinary long-term clinical follow-up protocols (7, 8).

It is estimated that the clinical incidence of aGvHD after HSTC accounts for 40% whereas the incidence of cGvHD can range from 13% to 80%; in particular, 13% in patients aged under 10 years, 28% in those aged between 10 and 19 years and over 40% in subjects aged over 20 years. Moreover, the incidence of cGvHD oral manifestations, in paediatric patients accounts for 45%. In general, the average survival rate in patients affected by GvHD is lower than 30% (9, 10).

Oral manifestations in GvHD patients

Although most GvHD symptoms mainly involve the skin, more than 90% of affected patients also develop a massive and progressive involvement of the oral mucosa (11).

Injuries affecting oral tissues, such as atrophy, erythema, ulcerations, mucositis and lichenoid lesions are associated with recurrent onsets of dysgeusia, xerostomy, trismus and salivary glands hypofunction and, combined, apparently emulate the clinical pictures of some autoimmune disorders (lichen planus, lupus erythematosus, scleroderma and Sjögren's syndrome). For this reason, GvHD is increasingly associated with oral precancer diseases or even malignant cancers (9, 12).

Unlike aGvHD, whose onset occurs approximately 2-3 weeks after the transplant with some clinical manifestations like erythema, erosion and ulceration of the oral mucosa, the pathological modifications induced by cGvHD can be recognised only after 70 post-transplant days (13). These modifications are clinically similar to those characterising the acute form, but typical protruding white lesions, patched and with smooth red striations also appear next to them, similar to those found in lichen planus, thus characterised by sclerotic mucosal changes and a reticular, erythematous or ulcerative anatomo-pathological impairment (11). Finally, the persistent salivary function reduction, leads to oral disorders: reduced mobility of the stomatognathic system, sensitivity or pain associated with the consumption of spices, alcohol and aromatizers (mint aroma in oral hygiene products), higher incidence of developing decay disorders, oral candidiasis and objective difficulty in swallowing, feeding and articulation of words (14, 15).

Clinical case

Patient M.H., aged 12, male, Iraqi nationality, came under our observation at the Outpatient Department of Paediatric Dentistry of the Tor Vergata University at the PTV, Policlinico di Tor Vergata in Rome. Being affected by a severe form of aplastic anemia, four months before he underwent Hematopoietic Stem Cell Transplantation (HSCT) from a compatible donor at the Mediterranean Institute of Hematology (Istituto Mediterraneo di Ematologia, PTV - Rome).

He had been reporting, for about one month, the occurrence of generalised algic symptoms in the oral cavity with concomitant onset of pathological concretions involving the skin and appendage structures, diagnosed as clinical expressions of the chronic form of the Graft versus Host Disease (cGvHD).

At the extra-oral examination the patient showed thin, subtle and fragile hair, eye-dryness and clear lichenoid and sclerodermic alterations of the face skin, localised in the areas around the eyes, nose, mouth and chin (Figs. 1, 2).

These injuries appeared like protruding, hypo- or hyperpigmented, sclerotic and scarcely hydrated areas, characterised by the presence of flaking epithelial cells scales accompanied by a widely-spread mucosal erythema (Fig. 3).

In particular, patient hands had nails with clear and widely spread itching erosions characterised by scaling phenomena of chronic flaking associated with onychlysis (Fig. 4).

The face was characterised by the facies typical of individuals affected by thalassaemia major: dilat-

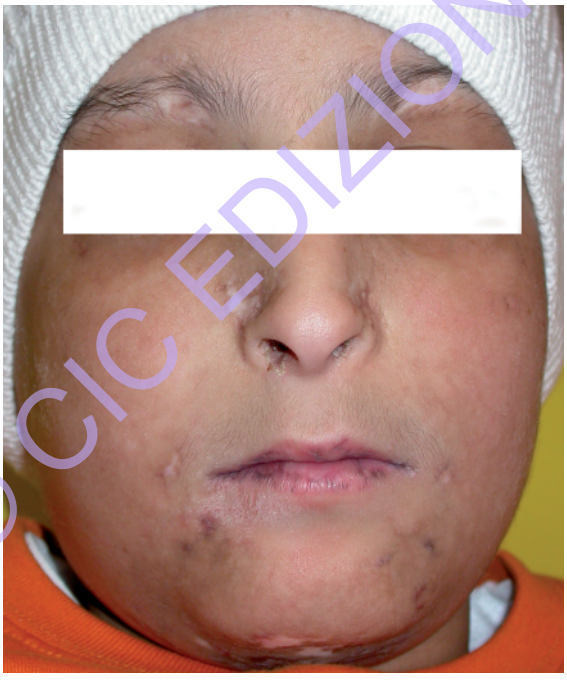

Figure 1
Frontal view: lichenoid and sclerodermic alterations of the skin face.

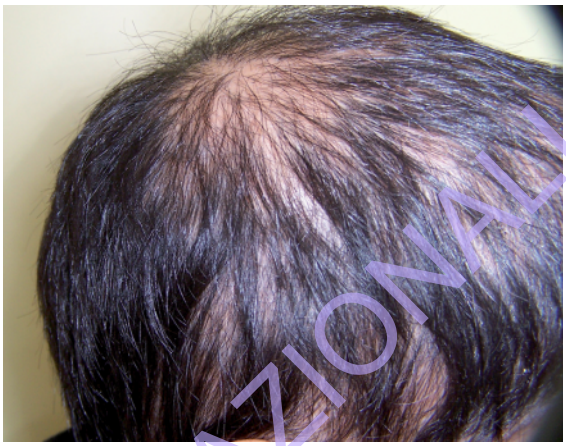

Figure 2
Thin, subtle and fragile hair.

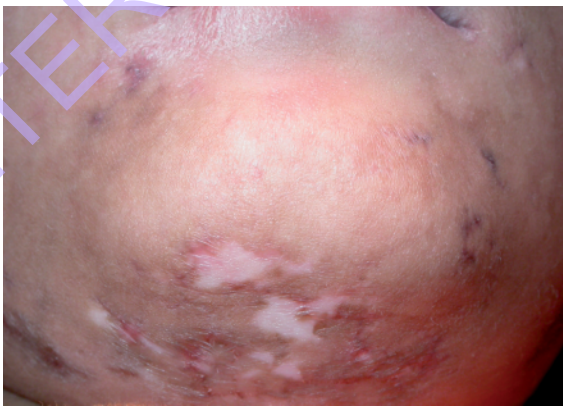

Figure 3
Protruding, hypo- or hyperpigmented, sclerotic areas of the chin.

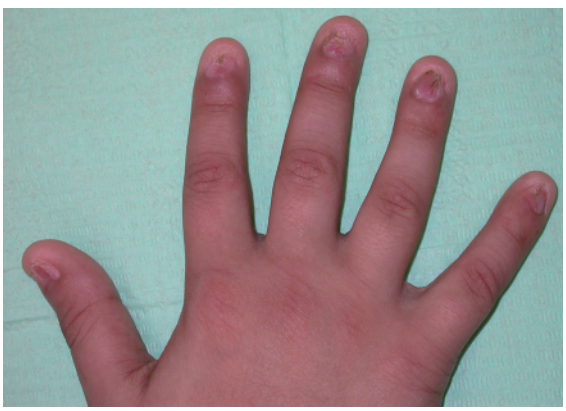

Figure 4
Spread erosions, onychlysis and flaking phenomena of the nails.

ed and thickened cranial bones (brush skull), with prominent frontal and rear eminences, sunken nose root, swollen eyelids, hypertrophy of the superior maxillary with convex cheekbones, high lip retraction, superior dental arch protrusion, increased mandibular diameter and consequent malocclusion (Fig. 5).
At the infra-oral examination, a contraction of the buccal fissure induced by the sclerosis of the face epithelium and mucous membranes was observed, together with a reduced mobility of the lip mucosa and tongue soft tissues, due to the development of severe fibrotic phenomena, to the extent of hindering clinical assessment manoeuvres and making the examination painful (Fig. 6).
The oral cavity was affected by a severe functional and aesthetic impairment, characterised by the presence of erosive lesions on the enamel surface, white spots, destructive decay processes, root residues of deciduous teeth, aphtous ulcerations, vesicular eruptions similar to herpes lesions and violet lichenoid reactions spread on the tongue, buccal and gum mucosa, as well as a scarce oral hygiene (Figs. 7, 8).

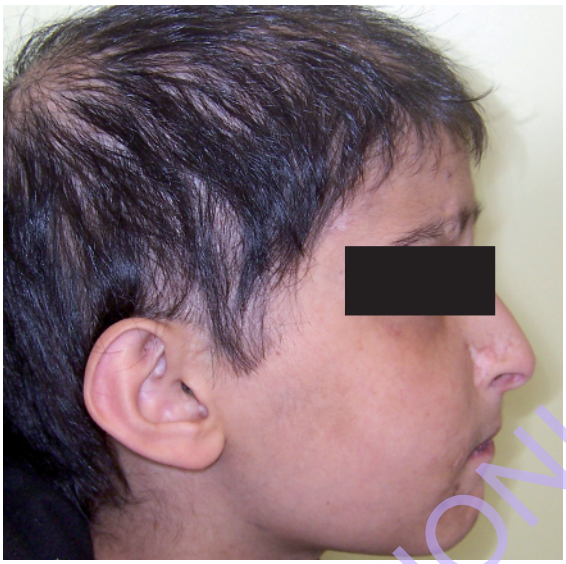

Figure 5
Lateral view: sunken nose root, high lip retraction.

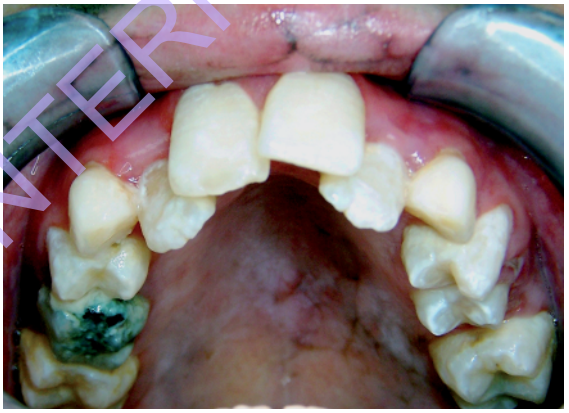

Figure 7
Compromission of the hard dental tissues.

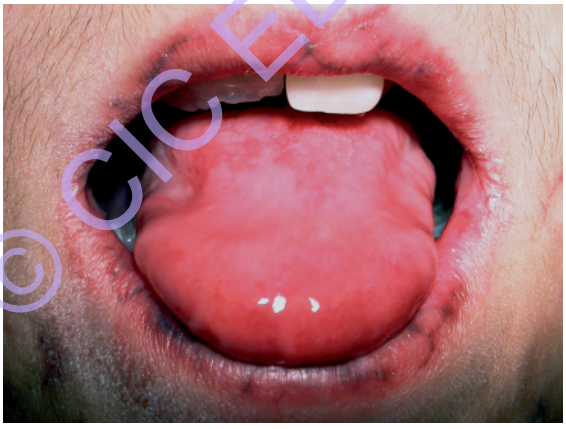

Figure 6
Contraction of the buccal fissure and reduced mobility of the lip mucosa and of the toungue.

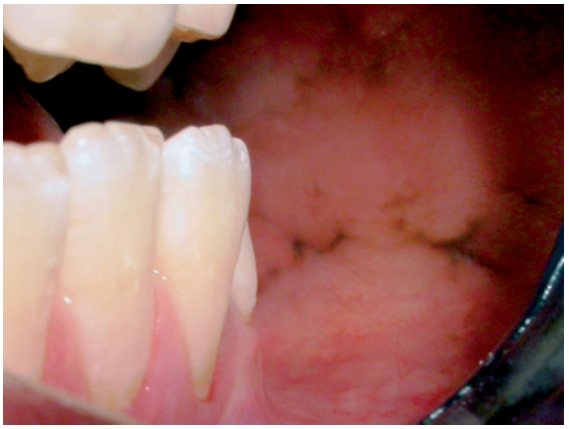

Figure 8
Spread violet lichenoid lesions of the buccal mucosa.

Moreover, the oral mucosa was depigmented, dry, pale and atrophic and was characterised by the presence of erosive plaques and ulceration lesions on the adhering gum or on mouth mucous membranes.
Aspecific superficial lesions were detected on the adherent mucosa of the palate, and the tongue was affected by a form of atrophic glossitis characterised by the presence of smooth, depapillated and confluent areas, similar to islets, delimited by an ulcerative lesion spread on the whole ventral part of the tongue back (Fig. 9).
It was possible to detect the involvement of the salivary glands, confirmed by the high reduction in the saliva flow, overall dryness and by the pale and atrophic mucosa.

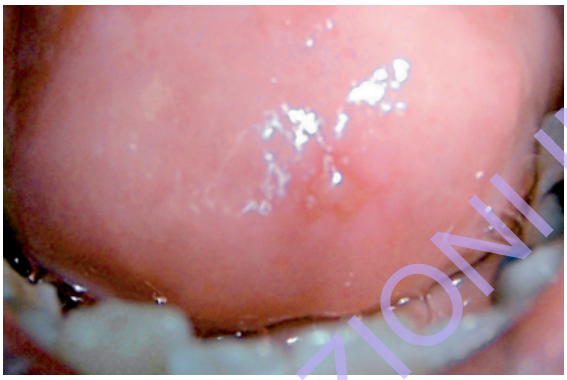

Figure 9
Ulcerative lesion on the ventral part of the tongue.

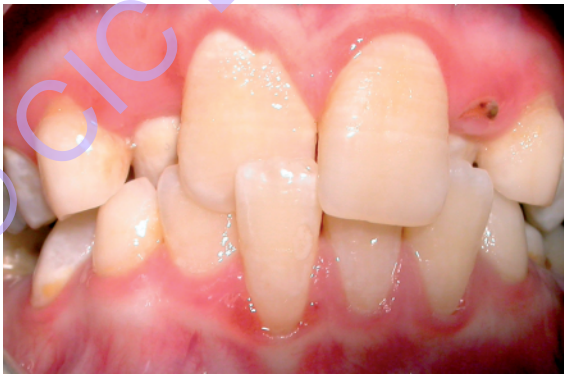

Figure 10
Dental malocclusion, frontal view.

Moreover, generalised lesions of the oral mucosa were identified, characterised by clear signs of a pronounced atrophy and a widely-spread erythema and ulcerations localised exclusively at the level of non-keratinised mucous membranes (oral floor, buccal, lip membranes and tongue).
As for the occlusion pattern, the patient showed a structural malocclusion, characterised by the presence of a superior maxillary skeletal contraction, made evident by both the cross-bite of the central right incisor and of the two superior lateral incisors and by the retraction of the superior lip ("rodent-like *facies*"), associated with an Angle class II with dental-alveolar discrepancy of the lower arch (Fig. 10).
Finally, in the left inferior emiarch, on the vestibular side of the molar region, a particular mucous alteration of the adherent gum was observed, in the form of an asymptomatic plaque, embedded in the hyperpigmented central part.
As for the therapeutic protocol, a bioptic drawing was performed (incision biopsy) of the mucous area affected by the pathologic alteration and of a part of the surrounding integral tissue suggesting a clinical diagnosis of chronic GvHD (Fig. 11).
The histopathological examination of this clinical report showed instead the presence of histological lichenoid-like changes, hydropic degeneration of the basal epithelial layer, apoptotic bodies, lym-

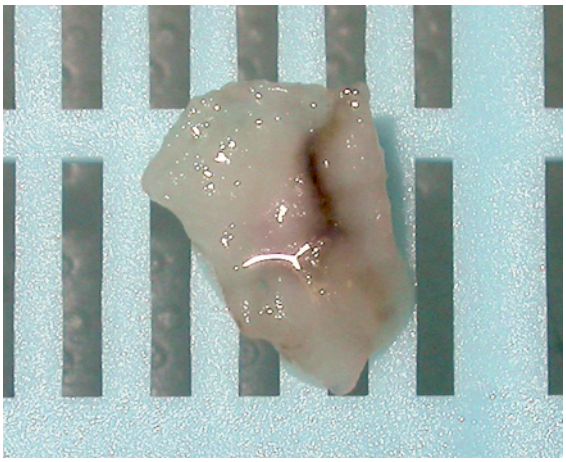

Figure 11
Bioptic drawing of the iperpigmentated lesion.

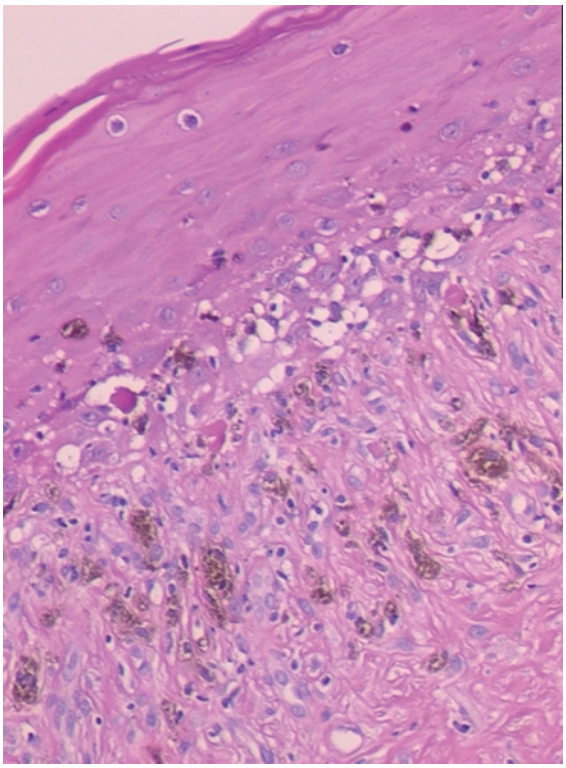

Figura 12
Histopathological examination: acute grade 1-2 GvHD (Lerner 1974).

phocyte infiltrate and total or focal separation between connective tissue and epithelium, typical of the acute grade 1-2 GvHD form (according to Lerner 1974) (16) (Fig. 12).

Discussion

GvHD is one of the most important complications in bone marrow transplantation. It affects specific target organs like skin, liver, gastrointestinal tract, oral mucosa and salivary glands and is accompanied by aspecific symptoms such as fever and weight loss. In particular, the oral form of GvHD is present in 80-90% of patients affected by systemic GvHD (17).
In most cases, oral lesions stand for the leading or even the only GvHD manifestation (18).

The patient enrolled in this study showed severe oral injuries, signs of typical hystopathological alterations (atrophy, erythema and lichenoid reactions) precisely induced by GvHD, as well as specific oral manifestations associated with injuries to face, hands and gastric mucosa, and aspecific generalised oral pain. Therefore, it is evident that the functional impact of GvHD oral injuries is so severe that the overall framework of disorders, associated with pain, prevents the patient from adequately feeding himself, with consequent feeding restrictions, high body weight reduction and delay compared to the normal growth and bone development reference tables (14, 19).
The GvHD diagnostic criterion encompasses signs and symptoms that are complete enough to establish the GvHD diagnosis, confirmed by local biopsy or diagnostic examinations of other injured organs (skin, appendage structures, oral mucosa, eye mucosa, oesophagus and connective tissues) (20, 21). The mucous membrane biopsy is useful both to determine the histological form and to establish the therapeutic approach of choice (22).
In the reported case, in the clinical examination a chronic GvHD form was hypothesised, which, instead in the anatomopathological assessment turned out being of an acute kind.
The abnormal bone growth of the face and of the high alveolar arch, which occurred very early in the dental-skeletal development, when chronic anemia triggers erythropoiesis which expands at the level of the bone marrow in areas in which it is normally absent, has lead to consequent alterations in the bone structure and shape of the cranial-facial district (23). The consequent onset of this malocclusion pattern is mainly due to the degree of disproportion existing between lower jaw and superior maxillary, induced by the forward and downward extension of the maxillary alveolar process that is also affected by a significant skeletal contraction of the premaxilla with cross-bite of incisors and a marked retraction of the higher lip ("rodent-like *facies*") (24).
The morpho-structural alterations of the cranial-face district can be largely promptly prevented by means of a transfusion therapy starting in the very first months of life and then in the school-age, fol-

lowed by an early interceptive orthodontic intervention treatment (23, 24).
As, at present, specific standardised clinical protocols are still lacking, the multidisciplinary approach must be, anyway, primarily focused not only on the reduction and elimination of pain symptoms, but also on the prevention and treatment of soft and hard tissue lesions in the oral cavity as well as on the resumption of normal feeding (23).
It is widely known that systemic therapy based on immunosuppressive drugs can lead to many side effects, whereas local therapies offer the possibility to administer more drugs like topic corticosteroids (desametasone), clorexidine 0.2%, bicarbonate and anaesthetics solutions (lidocaine), reducing systemic complications (25, 26).

Conclusions

Paediatric patients affected by neoplastic disorders and those affected by haematological non-neoplastic disorders undergoing HSCT protocols, frequently develop oral lesions, some of which are so severe to impair normal swallowing, feeding and speech (26).
Although, over the last years, scientific research has optimised hematopoietic stem cell transplantation techniques and procedures, the Graft-versus-Host Disease still accounts for the most severe and frequent complication, still affecting today approximately 20-50% of patients undergoing HSCT (15).
Therefore, early oral diagnosis plays a pivotal role as it allows to promptly detect the initial phases of this dynamic and complex disease and to set up a multidisciplinary treatment plan, which is essential to improve the quality of life in these patients (17).

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