Making sense of mouth ulceration: recurrent aphtous stomatitis

Crispian Scully[1]

Drug-induced ulceration

A range of drugs can cause oral ulceration (Table 1), so it is therefore important for the clinician to take a comprehensive drug history and always consider whether a drug may be behind the problem.

Clinically, there is rarely any particular feature (Figure 1). The diagnosis is from the history and by exclusion. A high index of suspicion is needed. Management is by avoiding the offending drug.

Mucositis

Chemotherapy (CTX) often causes acute injury to mucosae, affecting the mouth and whole gastrointestinal tract. CTX activates inflammatory pathways (such as the NF-kB pathway) and release cytokines, such as TNF-alpha, IL-1 and IL-6.

Most patients on high-dose CTX develop severe oral mucositis within a week of starting treatment, especially with CTX using:

- Cisplatin
- Etoposide
- Melphalan.

It can also be an issue with other CTX, especially anthracyclines (bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin, mitoxantrone), antimetabolites (cytarabine, fluorouracil, floxuridine, methotrexate, thioguanine) and antimitotic agents (taxanes such as docetaxel and paclitaxel; vinca alkaloids such as vinblastine and vindesine).

Clinical features of mucositis are widespread erythema, erosions/ulceration, swelling, and atrophy.

Diagnosis is from the history. Lesions in the cancer patient that can complicate the diagnosis of mucositis include fungal and viral infections as well as neutropenic ulcers.

Management is crucial since many patients find oral mucositis the most debilitating and troublesome adverse effect of cancer therapy. In addition, some find that although opioid analgesics are needed, they do not always adequately relieve pain, and can lead to other issues such as dry mouth and constipation.

There are few randomised controlled studies, and the available prophylactic and therapeutic strategies are limited, but discomfort from mucositis can be further reduced by:

- Excellent oral hygiene
- Oral cryotherapy using ice popsicles
- Exposure to soft laser
- Systemic administration of keratinocyte growth factor (palifermin).

Emergent agents being trialled for amelioration of the suffering of mucositis include buprenorphine transdermal patches for analgesia.

Graft-versus-host disease

Graft-versus-host disease (GVHD) may be a complication of bone marrow transplant or haematopoietic stem cell transplant (HSCT). This transfers T lymphocytes that perceive host tissues as antigenically foreign via HLA and other antigens, and mount an immune attack on the host, the transferred T-cells producing cytokines, including TNK-alpha and IFNγ.

Acute GVHD appears between 10 and 100 days post-transplant, is seen in about 60% of transplant survivors and may cause mouth ulceration. Acute GVHD affects

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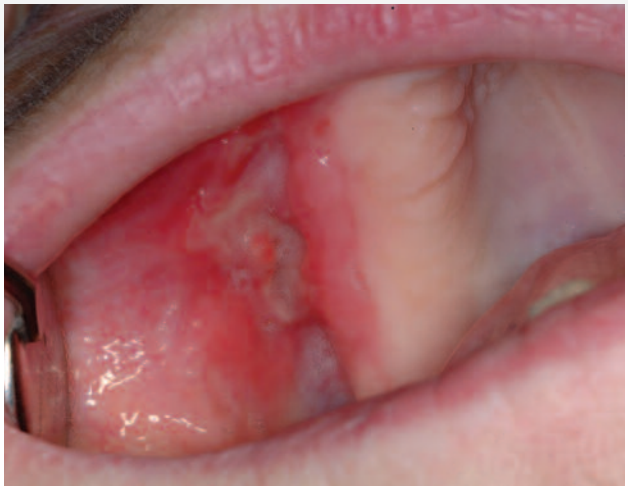

Figure 1: Drug-induced ulcer

mainly the liver, gastrointestinal tract and mucocutaneous tissues, and can be lethal. Therefore, prophylactic immunosuppressive therapy using methotrexate and ciclosporin is usually used for the first 100 days post-HSCT.

The oral manifestations of acute GVHD are difficult (or impossible) to differentiate from chemotherapy-induced mucositis. Acute GVHD is treated with high-dose immunosuppressive therapy.

Chronic GVHD may follow acute GVHD, or may arise ab initio, occurs after 100 days post-HSCT and affects around 50% of patients. Chronic GVHD can cause mouth ulcers and involves multiple organs – mainly the liver, gastrointestinal tract, eyes and skin.

In most cases (80%), oral lesions appear, including:

- Ulceration
- Lichenoid lesions
- Infections, especially candidosis
- Hairy leukoplakia
- Sclerodermatous syndrome and hyposalivation
- Ciclosporin-induced gingival swelling.

Chronic GVHD is treated with high-dose immunosuppressive therapy.

Management of orofacial lesions in acute or chronic GVHD is mainly with:

- Analgesics (morphine, buprenorphine or hydromorphone)
- Oral hygiene measures, including non-alcoholic chlorhexidine mouth rinses
- Artificial saliva (mouth wetting agents), xylitol chewing gum or pilocarpine
- Topical azathioprine or ciclosporin
- Nystatin or fluconazole suspension
- Growth factors.

Table 1: drugs implicated in oral ulceration

Alendronate
Anticonvulsants
Biologic agents (mainly anti-TNFs)
Cytotoxic agents
Everolimus (and mTOR inhibitors)
Mycophenolate
Nicorandil
NSAIDs
Tiotropium
Others (many)

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Disclosure

This series offers a brief synopsis of the diagnosis and management of mouth ulceration – a complex topic that includes common disorders, and less common but life-threatening conditions. It does not purport to be comprehensive, and the series may include some illustrations from books written or co-authored by the author and colleagues from UK and overseas, published by Elsevier-Churchill Livingstone, Wiley-Blackwell, or Informa/Taylor & Francis – all of whose cooperation is acknowledged and appreciated.

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