

# The non-healing extraction socket: a diagnostic dilemma – case report and discussion

## Abstract

**Statement of the problem:** Delayed healing, or failure of the alveolus to heal post exodontia, is not an uncommon finding in both primary care and hospital practice. Local factors dominate and the majority of cases are the result of clot dissolution, secondary infection, foreign bodies, etc. However, potentially life-threatening, malignant lesions complicating healing can be overlooked and underestimated due to their rare occurrence.

**Purpose of the review:** This article presents a contemporary review of the normal physiological process that directs healing within the extraction socket and a differential diagnosis for delayed healing or failure of healing following extraction, with guidance on appropriate management.

**Method:** A case report of a squamous cell carcinoma presenting in the clinical setting of a non-healing extraction socket, and a discussion of local and systemic factors that may interfere with healing, are presented.

**Conclusion:** The aetiologies of delayed healing and failure of the extraction site to heal are diverse, and the process can be affected by local and systemic factors alike. Given that neoplastic lesions are relatively rare, it is therefore all the more important for GDPs to remain cognisant of the diagnostic red flags that may raise suspicions of a mitotic lesion to ensure that appropriate referral pathways are instituted.

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## Introduction

Although the healing of extraction sockets is generally a rapid and uncomplicated process, delayed healing, overt infection, or failure of recent exodontia sites to heal can occur. Delayed healing is reported to occur in less than 11% of all extractions.<sup>1</sup>

A variety of factors may be implicated and the dental clinician must be aware pre-operatively of both local and systemic influences. The vast majority of cases are the result of innocuous, local factors such as dry socket or infection.<sup>1</sup> However, the potentially life-threatening, malignant lesions complicating this phenomenon can be underestimated.<sup>2-8</sup> Therefore, it is incumbent on dental professionals to familiarise themselves with the normal inflammatory and reparative processes involved in the restitution of mucosal continuity which follow extraction, and the potential pathological lesions that interfere with healing. Failure of an extraction socket to exhibit satisfactory signs of healing in a timely manner (within three to four weeks) warrants urgent referral to an oral and maxillofacial surgeon for investigation.

## Normal healing of the extraction socket

The extraction socket, like any other wound associated with tissue loss, heals by secondary intention.<sup>9</sup> There is a well-defined, orderly sequence of biological events, which restores the continuity of the alveolar mucosa and bone following exodontia.<sup>10</sup> The socket fills with blood, which coagulates to produce a loosely adherent clot. Platelets within the clot retract, causing the gingival tissues to collapse into the clot-filled alveolus. The clot then continues to stabilise by fibrin cross-linking within the first 24 hours of the extraction. This is the rationale behind deferring rinsing for one day post-operatively.<sup>11</sup>

During the next 48 hours the clot is broken down by fibrinolytic activity of the enzyme plasmin.<sup>12</sup>

After approximately five days, ingrowth of fibroblasts from the socket wall occurs and angiogenesis results in the formation of capillaries, fixing the clot to the socket wall with granulation tissue. Fibroplasia (production of fibrous tissue) ensues, with eradication of the fibrin by macrophages and replacement with granulation tissue.<sup>13</sup> Gingival epithelium then proliferates and grows over the intact clot below the surface debris.<sup>14</sup>

Over the next two weeks, a variable amount of osteoid is produced by induced mesenchymal cells, and osteoprogenitor cells in the residual periodontal ligament.<sup>15</sup> This results in the formation of woven bone, which is then remodelled by subsequent osteoblastic and osteoclastic activity, resulting in the formation of mature lamellar bone. Gradually, the cortical bone of the empty socket (the radiographic lamina dura) is replaced and the socket filled by trabecular bone. Healing is complete at approximately three months post extraction. This typically expeditious process is attributed to the abundant vascular supply of the alveolar process and accompanying periosteum, the responsiveness of the gingival epithelium, and the rapid turnover of periodontal connective tissue elements.<sup>16</sup>

## Case report

### Clinical presentation

A 55-year-old female presented to the department of oral and maxillofacial surgery at the Dublin Dental University Hospital, on referral from an oral surgeon, regarding a non-healing socket of three months' duration, following surgical extraction of the lower right third molar. The presenting complaint was of severe pain in the region of the extracted tooth. The medical history

included rheumatoid arthritis, and the patient had a history of oral bisphosphonate use and adalimumab therapy (a tumour necrosis factor (TNF)-inhibiting anti-inflammatory medication).

Clinical examination revealed a tender and enlarged right submandibular lymph node extra-orally and trismus was observed. There was a subjective sensory alteration of the right tongue; however, clinical examination revealed no objective sensory deficit in the third division of the trigeminal nerve. Upon intra-oral examination a non-healing extraction socket in the lower right third molar region was detected with granulation tissue filling a small distinct cavity. Radiographically there was an area of diffuse bone loss, related to the extraction socket of the lower right third molar extending posteriorly. The lesion was non-corticated, with ragged edges, and of ill-defined shape (Figures 1 and 2).

### Differential diagnosis

At presentation, the differential diagnosis included osteomyelitis (the possibility of a rare persistent infection such as actinomycosis was considered given the history of adalimumab therapy),<sup>17,18</sup> medication-related osteonecrosis of the jaw, and intra-oral malignancy.

### Investigations

The non-healing extraction site was explored surgically and soft tissue curetted from the bony socket. This was sent for histopathological examination and fragments of moderately differentiated keratinising squamous cell carcinoma were detected. Imaging, which included positron emission tomography (PET) and computed tomography (CT) scanning, revealed a significant lesion within the right mandible. The tumour was staged as T4N0M0 according to The American Joint Committee on Cancer (AJCC) Tumour-Node-Metastasis (TNM) cancer staging system.<sup>19</sup>

### Management

The cancer was managed in the first instance with surgical resection (hemimandibulectomy, partial glossectomy and neck dissection) supplemented with radiation therapy post-operatively. The reconstructive phase of the surgery involved a vascularised free fibular flap for bony reconstruction.

### Discussion

This case report highlights the need for prompt referral of suspicious lesions, and early detection of potential malignancies. Cancer of the head and neck is a major health problem worldwide, accounting for 6% of all cancers.<sup>20</sup> In Ireland, oral and pharyngeal cancer represents approximately 4% of all cancer registrations and 1.5% of all cancer deaths.<sup>21</sup> Alveolar ridge carcinomas, although poorly studied, are purported to comprise 9% of all oral squamous cell carcinomas (OSCCs).<sup>22</sup>

OSCC can present initially as an asymptomatic red or red and white (erythroleukoplakic) patch or plaque. Untreated, it then progresses to an indurated (hard) ulcer or lump with irregular margins.<sup>23</sup> A much less common manifestation of oral cancer is delayed healing of the extraction socket, as presented in this case report. Accordingly, malignant tumours are associated with a variety of clinical signs and symptoms including pain, swelling, mobile teeth, and bleeding.<sup>23</sup> A similar clinical picture is also apparent when inflammatory dental pathology is encountered.<sup>24</sup>



FIGURE 1: Orthopantomogram radiograph showing bony defect at site of lower right third molar extraction socket.

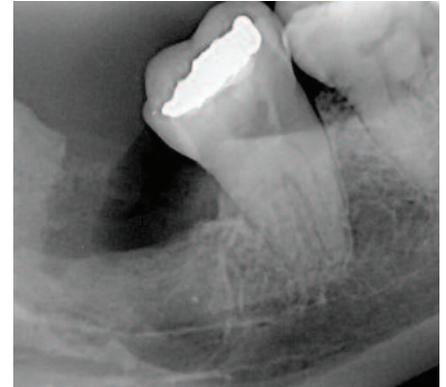


FIGURE 2: Intra-oral peri-apical radiograph of lower right third molar region showing ragged bony margins and aberration from the normal radiographic appearance of the healing extraction socket.

This can confound the diagnosis of an early invasive tumour as they have features that mimic periodontal disease and alveolar abscesses.<sup>5</sup> In cases where OSCC presents post exodontia, it is likely that the presence of a tumour is overlooked and misdiagnosed due to similarity between this condition and common dental pathology. It has been reported, worryingly, that tooth extraction at the site of an OSCC may increase the risk of lymphatic metastasis, thus worsening the prognosis.<sup>3,25,26</sup> However, other authors argue against this supposition.<sup>25,27</sup>

Malignant lesions arising from the oral mucosa, the intraosseous tissues, and the maxillary sinus/paranasal sinuses/nasal cavity may all interfere with the orderly sequence of wound healing following exodontia. Indeed, failure of healing in an extraction socket may be the initial presenting feature of some of the more insidious malignancies, such as antral carcinoma or metastases from occult primary tumours.<sup>28,29</sup>

A neoplastic lesion, particularly an aggressive one, will result in tissue necrosis.<sup>9</sup> This, and the presence of the tumour itself, will serve as a barrier to the ingrowth of reparative cells, complicating the healing process. Additionally, in a similar manner to foreign material in the wound, necrotic tissue serves as a protected niche for bacteria. Malignant tumours may also cause ischaemia if complicating the site of an extraction, again interfering with the healing process.<sup>9</sup>

### Other factors affecting healing

Delayed healing of an extraction socket should always carry an index of suspicion for the treating clinician. However, the occurrence of a malignant lesion complicating healing is rare and the focus of this discussion now turns to the differential diagnosis when presented with failure of the extraction site to adequately heal. The role of the general practitioner in the management of delayed healing following exodontia is the exclusion of common, innocuous causes. Once these common causes of failed healing have been accounted for and excluded, referral to a specialist centre for investigation is advised.

Delayed healing or failure of an extraction socket to heal satisfactorily can be the result of either local or systemic factors. These factors may impair the quality of both inflammation and repair within the tissues (Table 1).

#### Local factors

The extraction socket can be influenced by local factors in a similar manner to

other wounds in the body,<sup>9</sup> including infection, mechanical factors, foreign bodies, and the size and nature of the wound. The circulatory status, and vascular supply to the anatomical site, also have a profound effect on wound healing.<sup>30</sup>

Table 1: Considerations in non-healing extraction sockets.

Local	Systemic
Alveolar osteitis (dry socket)	Malnutrition
Residual cysts	Drugs, e.g., steroid hormones
Periodontal infection	Age
Infected granulation tissue /foreign body	Immunosuppression
Malignancy: ■ oral mucosal; ■ intraosseous; ■ maxillary sinus/nasal cavity; and, ■ secondary metastases.	Blood dyscrasia
Osteomyelitis	Chronic diseases (renal disease, liver disease)
Osteoradionecrosis (when the radiation field encompasses the alveolus)	Endocrinopathies, e.g., diabetes mellitus
Osteochemonecrosis (including medication-related osteonecrosis of the jaws)	Smoking
Uncompressed, fractured cortical plates	Salivary hypofunction
Alveolar bone sequestra	
Oro-antral communications and fistulae	
Infective maxillary sinus disease (bacterial and fungal)	

### *Alveolar osteitis (dry socket)*

Dry socket is the most common postoperative complication after tooth extraction, with an onset at two to four days after surgery.<sup>31,32</sup> It is defined by Blum as “postoperative pain inside and around the extraction site, which increases in severity between the first and third day after the extraction, usually caused by a partially or totally disintegrated blood clot within the socket”.<sup>33</sup> The reported incidence of this condition ranges from 1-4% of extractions, increasing to 45% for mandibular third molars.<sup>33-36</sup> In alveolar osteitis, healing is delayed because tissue must proliferate from the circumferential gingival mucosa, which takes longer than the normal organisation of a blood clot.<sup>33</sup>

### *Foreign bodies and secondary infection*

Foreign material is anything the host immune response views as ‘non-self’, including bacterial by-products, suture material, socket dressings, etc. This material acts as a haven for bacteria by sheltering them from host defences and thus promoting infection.<sup>37</sup> Foreign material is also antigenic and can trigger a chronic inflammatory reaction that retards healing. The clinical relevance of these points extends from selection of suture material to arguments against the prophylactic use of socket dressing.<sup>32,33</sup> Secondary infection will perpetuate the destructive elements of the inflammatory process. This, coupled with the production of bacterial enzymes, leads to cell death and tissue necrosis, delaying normal healing.<sup>37</sup> In a prospective clinical trial of 311 uncomplicated, routine extractions the incidence of delayed healing due to secondary infection was reported at 1.6%.<sup>1</sup>

### *Residual cyst*

A residual radicular cyst arises from epithelial remnants (the rests of Malassez) stimulated to proliferate by an inflammatory process resulting from pulpal necrosis of a non-vital tooth that has since been extracted.<sup>38</sup> The natural history begins with a necrotic tooth, which remains *in situ* long enough such that chronic peri-apical pathology (for example a radicular cyst) becomes established. Eventually the tooth is extracted without consideration of the peri-apical pathology, persisting within the alveolus as a residual dental cyst.<sup>39</sup> The residual cyst is often an incidental radiographic finding, but sometimes it can become painful in case of secondary infection, or the pathological entity may present as delayed healing of an extraction socket.<sup>40</sup> This illustrates the possible sequelae when judicious removal of peri-apical pathology and radiographic follow-up are not undertaken following the extraction of a necrotic tooth.

### *Osteomyelitis and osteonecrosis*

Osteomyelitis is described as an inflammation of bone and bone marrow. It may develop in the jaws following a chronic odontogenic infection or for a variety of other reasons,<sup>41</sup> and can be acute, sub-acute or chronic, each resulting in a totally different clinical picture. Osteomyelitis forms part of the differential diagnosis when considering delayed/failure of healing in an extraction socket.<sup>42</sup> Osteonecrosis manifests as lesions of necrotic and exposed bone in the oral cavity that persist for at least eight weeks.<sup>42,43</sup> It may be associated with a number of different predisposing conditions, most commonly radiation therapy to the head and neck and medications such as bisphosphonates, denosumab and others.<sup>42,43</sup> Osteonecrosis can significantly impair the healing process following exodontia, and may require surgical intervention in severe cases.

### *Oro-antral fistula*

An oro-antral fistula (OAF) is a pathological communication between the oral cavity and the maxillary sinus.<sup>44</sup> It arises most often after extraction of posterior maxillary teeth due to the intimate anatomical relationship between the apices of the molar and premolar teeth and the maxillary antral floor.<sup>45</sup>

In contrast to the oro-antral communication (OAC), OAF is categorised by the presence of an epithelial tract arising from the oral mucosa and/or from the antral sinus mucosa that, if not removed, can inhibit spontaneous healing.<sup>38</sup> Repairing this defect is important to avoid food and saliva contamination that may establish and perpetuate bacterial infection, impaired healing, and chronic sinusitis.<sup>46</sup>

### **Systemic factors**

#### *Nutrition*

The patient’s nutritional state is a potent factor in determining the outcome of wound healing.<sup>47</sup> The undernourished patient is immunocompromised, which predisposes to wound infection that delays healing.<sup>48</sup> Additionally, deficient protein intake may inhibit collagen formation and delay healing.<sup>49</sup> Vitamins A and C, and zinc, are also important micronutrients implicated in wound healing, as well as haematinics such as iron, folate, and vitamin B12.<sup>47,48,50,51</sup>

#### *Steroid hormones*

Glucocorticoid hormones (such as prednisolone) inhibit collagen synthesis and inflammation, and impair immunity. Used therapeutically they can therefore lead to delayed healing.<sup>52</sup>

#### *Age*

Increasing age is often stated to be a factor affecting the efficacy of wound healing.<sup>53</sup> It is true that wounds tend to heal more rapidly in the young than in the elderly, but it is difficult to be certain that it is age *per se* that is exerting an effect, or whether delayed healing in the aged may be due to local vascular factors such as poor arterial perfusion.<sup>54</sup>

#### *Metabolic status*

The presence of a metabolic disease, such as diabetes mellitus, can affect wound healing.<sup>55</sup> Diabetes mellitus, especially if glycaemic control is poor, has an inhibitory effect on the healing process.<sup>56,57</sup>

There is an impairment of the neutrophil response to injury and infection. In addition, diabetics may suffer from poor vascular perfusion.<sup>58</sup> Other intra-oral effects of diabetes mellitus have been discussed elsewhere,<sup>59</sup> but the authors again emphasise the important role that the dentist has to play in its diagnosis. Delayed or impaired wound healing in the oral cavity should alert the general dental practitioner (GDP) to the possibility of an insidious, underlying systemic process such as diabetes mellitus.<sup>58</sup>

### **Conclusion**

There will be cases where, despite adequate surgical care, the extraction site will not heal. Delayed or non-healing extraction sites always require investigation.

The majority are the result of local factors such as alveolar osteitis and infection. However, the clinician must be aware that in certain circumstances a potentially life-threatening disorder may be driving this clinical presentation, as highlighted in this case report. Considering the latter scenario is a relatively rare

encounter in general practice, it is therefore of the utmost importance that GDPs remain cognisant of the signs and symptoms suggestive of invasive malignancy of the oral cavity and paranasal sinuses. Prompt referral and early diagnosis, once all other local and systemic factors impairing healing have been excluded, will correlate with a better outcome for the patient.

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