Non-Healing Extraction Socket: A Diagnostic Challenge for General Dental Practitioners

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Abstract

Introduction:

In the UK, more than 1.8 million extractions are performed annually. Healing after extraction is often uneventful, but there are rare cases where weeks or months pass and an extraction socket does not heal.

Aim:

The aim of this study is to provide a review of cases in which a non-healing extraction socket is attributed to a serious systemic disease or malignancy, or an adverse consequence of systemic therapy.

Methods:

PubMed, EMBASE, SCOPUS, ProQuest and Google Scholar databases were searched using the term 'non-healing extraction socket'. Results were subsequently restricted to humans and English language.

Results:

A total of 50 cases of extraction socket non-healing (28 females and 22 males with an average age of 55.2 years) were identified. The total number of extracted teeth was 71. Malignancy (primary and metastatic) was the most common definitive diagnosis followed by medication-related osteonecrosis of the jaw (MRONJ).

Discussion:

There are cases in which an extraction socket does not show any sign of proper healing even after a lengthy period. Some of these cases are caused by primary or metastatic cancer, or other serious disorders.

Conclusion:

Dentists should be vigilant when encountering a non-healing extraction socket as this may herald an undiagnosed serious disease or malignancy.

Dental extraction is one of the most common surgical procedures undertaken worldwide. For example, in England there were more than 1.8 million dental extractions performed for adults at primary care in the 12-month period ending in March 2023.[1] This constitutes about 8% of all dental treatments provided for adults in the primary care setting during that period. While the majority of dental (especially non-surgical) extractions will often be followed by uneventful healing, some patients may still experience common complications such as pain, swelling, bleeding, infection and trismus. There are also cases in which healing is delayed – the most common cause being alveolar osteitis (dry socket), which is characterized by continuous, severe, deep-seated 'bone' pain in or around the socket that usually develops 2-3 days following extraction, and is sometimes accompanied by halitosis.[2] Delayed healing can also be encountered in patients with certain systemic disorders e.g. alcohol-related liver disease and nutritional deficiencies.[3] However, there are cases (albeit rare) where weeks (even months) may pass and an extraction socket does not heal. In such instances, the attending dentist should consider a more sinister cause and refer the affected patient promptly.

The aim of this study is to provide a succinct review of cases in which a non-healing extraction socket is attributed to a serious systemic disease or malignancy, which may be unknown to the patient; or an adverse consequence of systemic therapy. Although there are several case reports and case series on this issue, there seem to be no collective reviews on the causes of the non-healing extraction socket. There is no intention to discuss every possible scenario, but rather to highlight a spectrum of causes which have been reported in the literature, to increase awareness among the general dental practitioners (GDPs)

Materials and Methods

PubMed, EBMASE, SCOPUS, ProQuest and Google Scholar databases were searched using the term 'non-healing extraction socket'. Results were then restricted to humans and English language. Any duplicates were removed. For the purpose of this review, only case reports and case series where authors have clearly reported that the non-healing extraction socket was due a serious local or systemic disease or therapy were included. Editorials, expert opinions, correspondences and letters to the Editor were all excluded.

Results

Thirty five (35) case reports and 3 case series were identified (**Error! Reference source not found.**). The total number of patients was 50: 28 females and 22 males at a female to male ratio of about 1.3: 1. The age of the patients ranged between 26 and 81 years, with an average

age of 55.2 years (SD=13.5) and a median age of 56 years. The total number of extracted teeth was 71 (some patients had more one tooth extracted) – more than half of these (58%; n= 41) were mandibular posterior teeth.

The indication for extraction was reported in 22 cases only - reasons were predominantly non-specific such as tooth mobility/looseness of teeth, swelling, periodontitis, pain, and infection. In one case, there was also pre-extraction paraesthesia of the right lower lip and chin in a female patient who was subsequently diagnosed with metastatic breast cancer to the mandible.

Malignancy was the most common definitive diagnosis (68%; n=34); of which 25 (73.5%) were primary and 9 (26.5%) were metastatic. The most common primary malignancy was squamous cell carcinoma (SCC) - 60% of all primary cancer cases (n=15). Of the identified metastatic malignancies, 3 originated in the lung, 2 in the breast, and the remaining metastasized from the liver, kidney and colon – one case each. This is in addition to one case of metastatic angiosarcoma in which the origin was not identified. Of note, 5 patients with later-established metastatic disease had not any prior history of malignancy. Patients with metastasis waited on average 3 months to be diagnosed with non-oral malignancy, with one patient waiting 6 months.

The second most common diagnosis was medication-related osteonecrosis of the jaw (MRONJ) affecting 10 patients – all of them were females. The most common underlying disease necessitating relevant medication in patients with MRONJ was metastatic breast cancer (n = 7). The remaining three patients with MRONJ had metastatic thyroid cancer, rheumatoid arthritis and osteoporosis. The most common drugs associated with MRONJ were zoledronic acid and denosumab – 3 cases each. The remaining definitive diagnoses were Langerhans cell histiocytosis (LCH), ameloblastoma, osteomyelitis, inverted maxillary papilloma, brown tumour of hyperparathyroidism and sarcoidosis, with one case each.

Table 1: Demography and diagnoses of patients with reported non-healing of an extraction site

	Female	**Male**
Number of patients (percentage)	28 (56%)	22 (44%)
Average age (years)	58.06	55.1
Diagnosis		
1. Primary malignancy		
Squamous cell carcinoma (SCC)	7	8
Ameloblastic carcinoma	1	1

Carcinoma cuniculatum	-	1
Neuroectodermal tumour of maxillary sinus	-	1
Rhabdomysacroma	1	-
Hodgkin lymphoma	-	1
Non-Hodgkin lymphoma (NHL)	1	1
Plasmacytoma	-	1
Malignant melanoma	1	-
2. Metastatic malignancy		
Breast	2	-
Lung	-	3
Colon	-	1
Kidney	-	1
Liver	1	-
Unknown	-	1
3. Others		
Medication-related osteonecrosis of the jaw (MRONJ)	10	-
Granular cell ameloblastoma of mandible	1	-
Langerhans cell histiocytosis (LCH) of mandible	1	-
Osteomyelitis	-	1
Brown tumour (hyperparathyroidism)	1	-
Sarcoidosis	1	-
Inverted papilloma of the maxillary sinus	-	1
Total	**28**	**22**

Discussion

In the majority of patients, healing after extraction is usually uneventful. The healing process begins immediately following extraction and continues for up to 6 months, during which it progresses through four stages (often overlapping in timing): haemostasis and coagulation, inflammatory, proliferative, and remodelling.[4]

As soon as a tooth is extracted, the socket fills with blood which then undergoes coagulation (usually producing a loosely adherent clot) to seal the empty socket from the oral environment.[5] Over the following week, the remaining epithelial rim (i.e. gingiva) at the coronal part of the empty socket begins to grow along the socket wall until it contacts epithelium from the opposing side of the socket, or otherwise reaches the granulation tissue bed (i.e. newly formed blood vessels surrounded by fibroblasts which usually forms within the clot) over which

the epithelium can migrate and ultimately merges with epithelium from the other side.[6] This results in a complete closure (i.e. sealing) of the socket in approximately 4 to 6 weeks.[2] It would, therefore, be prudent for a GDP to promptly refer cases where there is a complete absence of any sign of healing after 4 weeks (unless there is a history of taking antiresorptive or antiangiogenic medications – discussed later.)

It is, however, important to recognize that healing varies between patients, and is often affected by several local (e.g., disintegration of clot by physical action, infection or foreign body), and systemic factors (**Error! Reference source not found.**). The latter includes disorders which are often associated with reduced healing potential such as age, diabetes mellitus, systemic corticosteroids, chemotherapy, alcohol-related liver disease and nutritional deficiencies or anaemia.[3] Such conditions can be readily highlighted during taking of medical and social histories.

Table 2: Potential local and systemic causes of delayed and non-healing extraction sockets (*)

	Local Causes	**Systemic Causes**
Delayed Healing [2,3,5,7]	1. Alveolar osteitis (dry socket) 2. Local Infection (e.g. periodontitis or infected granulation tissue) 3. Foreign body (alveogyl remnants) 4. Alveolar bone sequestrum 5. Tobacco smoking	1. Old age 2. Obesity 3. Diabetes mellitus (particularly uncontrolled) 4. Smoking 5. Alcohol-related liver disease 6. Corticosteroid therapy 7. Chemotherapy 8. Malnutrition/Nutritional deficiency 9. Severe anaemia or blood dyscrasia
Non-healing	1. Osteomyelitis [8] 2. Radiation to the jaws 3. Primary malignancy e.g. SCC [5,9] 4. Neoplasms of maxillary sinus or nasal cavity [10] 5. Odontogenic tumour e.g. ameloblastoma [11]	1. Medication-related osteonecrosis of the jaw (MRONJ) [13] 2. Metastatic cancer [14] 3. Langerhans cell histiocytosis (polystotic and disseminated) [12] 4. Sarcoidosis [15] 5. Hyperparathyroidism

	6. Langerhans cell histiocytosis (monostotic) [12]	

(*) The list is not exhaustive

Primary intraosseous malignancies of the jaws are predominately carcinomas followed by sarcomas.[16] The former represents a rare type of malignancy affecting the jaws (the majority affect posterior mandible) which can be classified according to their histological subtype into 1) salivary gland carcinomas (e.g. mucoepidermoid carcinoma), 2) odontogenic carcinomas (e.g. ameloblastic carcinoma), and 3) squamous cell carcinomas which are the most common.[16,17] In the present review, as perhaps expected, 60% of all primary cancers were squamous cell carcinomas which indicates that oral cancer may have clinical presentations different to the classic picture (e.g. a persistent, solitary, indurated ulcer on the posterolateral border of the tongue with rolled margins.) (**Error! Reference source not found.** – adapted with permission from Richards et al. (2021)).[18] Indeed, Huang *et al.* reported that approximately 60% of patients with primary intraosseous squamous cell carcinoma (PIOSCC) of the jaw presented with a non-healing extraction socket.[19] Of note, PIOSCC is characterized by high recurrence and mortality rates,[20] which is reportedly equivalent to the prognosis of stage 4 SCC of the oral mucosa.[16]

Metastasis of non-oral malignancies to the mouth is rare, accounting for only 1-1.5% of all cancers in the orofacial region.[21] The most commonly reported primary sites associated with metastasis to the oral cavity are the lung, breast, kidney, and colon, which is consistent with the findings of this review -[22] Lung was the primary site of metastasis in 3 cases, and breast was in two. While metastasis often represents a sign of advanced cancer, and is commonly associated with spread to multiple organs, metastasis to the oral cavity may represent the first sign of cancer spread in as high as 25% of the cases according to some studies.[23] In the present review, only 4 patients with metastasis reported a prior or present history of cancer i.e. more than half of the patients had not been aware of their cancer. This potentially indicates that the oral cavity (and indeed a non-healing extraction socket) could be the first clinical manifestation of undiagnosed malignancy of other organs.

Clinical presentation of metastatic disease to the mouth can significantly vary between patients, and sometimes has features overlapping with other (more common) oral diseases e.g. pain, swelling, tooth mobility and bleeding. This makes it exceptionally challenging for GDPs to recognize such cases and act promptly, particularly for patients who do not report a history of cancer. Delay in diagnosis is thus likely as perhaps indicated in the present review with an

average of about 3 months, but was as long as 6 months. It would, therefore, be prudent that patients who present with sudden looseness of teeth, bleeding that is difficult to control, or progressive swelling, particularly in those with history of cancer; are monitored on a weekly basis following extraction, and referred promptly to a specialist care if no signs of healing are detected after 4 weeks - or 8 weeks in patients on antiresorptive or antiangiogenic therapy.[24]

Medication-related osteonecrosis of the jaw (MRONJ) is described as an area of exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks, where there is history of a current or previous treatment with antiresorptive or antiangiogenic agents, but with no history of radiation therapy to the jaws, or obvious metastatic malignancy to the jaws.[25] It is an uncommon, severe bone complication secondary to therapy with anti-resorptive (e.g. bisphosphonates and denosumab) or anti-angiogenic drugs (e.g. vascular endothelial growth factor (VEGF) inhibitors (bevacizumab)). There were 9 cases of MRONJ in this review and the culprit medications were mainly zoledronic acid and denosumab.

Oral Bisphosphonates are prescribed for management of osteoporosis, Paget's disease, osteogenesis imperfecta, fibrous dysplasia; as a prophylaxis to counteract the osteoporotic effects of glucocorticoids, or to prevent skeletal complications in patients with primary hyperparathyroidism and cystic fibrosis.[26] Intravenous BPs (e.g. zelodronic acid) are indicated to reduce symptoms and complications of malignancies that commonly resorb (e.g. multiple myeloma) or metastasize to bone (e.g. prostate, breast, lung).[24] Denosumab is a fully human monoclonal antibody against RANK ligand which inhibits osteoclast function and associated bone resorption. It is indicated for management of osteoporosis and for reduction of skeletal complications in patients with bone metastasis from solid tumours.[24] The exact mechanisms underlying MRONJ pathogenesis are still not fully understood, but the condition is likely to be multifactorial, and centred upon a reduced capacity for bone to remodel (in view of altered osteoclastic activity and reduced blood supply), with some interplay or influence by local (e.g. infection, microtrauma, inflammation) immunogenetics and response of innate and adaptive immunity.[27] The disease is limited to the jaw bones and the clinical manifestations resemble an osteomyelitis-type disease. These include unexplained dental pain, bone pain, tooth mobility, altered sensation, recurrent bone infection with local swelling and/or sinus formation and bony sequestration, pathological fracture and extraction socket non-healing [24] (Figure 2 – adapted with permission from Badr et al. (2017)) [28] Although dentoalveolar surgery (mainly tooth extraction) is the most commonly reported risk factor predisposing to MRONJ,[24] it is crucial to recognize that MRONJ is an adverse effect of treatment with anti-resorptive or anti-angiogenic medications, and although invasive dental treatment is associated with an

increased risk of developing MRONJ, it does not cause the condition.[26] Therefore, in order to obtain a valid consent all patients who have been taking anti-resorptive or anti-angiogenic medications should be warned to the risk of MRONJ before dental extraction regardless of the type or the route of medication. This could manifest as a non-healing socket as demonstrated in the present review; thus it is important to monitor the socket healing on a weekly basis, and refer if no signs of healing are clinically detectable after 8 weeks. Table 3 summarizes the main features of the remaining causes of extraction socket non-healing which have been identified in the present review.

Conclusion

Healing after dental extraction is almost always uneventful, although there are cases where healing is notably delayed either due to local factors, which can be identified via clinical or radiographic examination, or systemic causes which can readily be highlighted in the medical or social histories (**Error! Reference source not found.**). However, as indicated by some of the presently reported cases, it is sometimes impossible to recognise that a patient has an underlying disorder that will place them at risk of extraction site non-healing. In all instances of non-healing, it would be prudent for GDPs to always have a degree of suspicious for more serious causes when encountering such cases (**Error! Reference source not found.**), and to consider accurate and timely referral of the patient to a specialist centre/service - as not only might the local disease require particular investigation (e.g. histopathological examination of tissue), but the underlying cause identified - and properly managed. The role of the GDPs is, therefore, not necessarily to determine the diagnosis, but to take appropriate actions when they encounter a non-healing extraction socket even in an apparently healthy young patient. This will not only allow instigation of treatment, that may in turn prove to be lifesaving; but will also reduce any potential medico-legal claims. Box 1 provides a case study published by an indemnity provider in which a delayed referral of a patient with a non-healing extraction socket, with a later-established diagnosis of squamous cell carcinoma, led to a claim of negligence and substantial compensation.

Recommendations

General dental practitioners can play a key role in expediting the diagnosis of a serious systemic disease or malignancy, such as the case with patients who present to them with extraction socket non-healing. This is crucial as otherwise any delay (a professional delay in

this case) in the diagnosis and timely management of such disease could result in more invasive treatment (which is also costly) thus increasing the likelihood of significant morbidities. Therefore, the following steps are recommended for GDPs when encountering cases of extraction site non-healing:

1. Thorough dental, medical and social histories
2. Careful extra-oral examination e.g. palpation of the regional lymph nodes or assessment of mouth opening (in case of trismus)
3. Careful examination of the extraction socket and the surrounding area under sufficient light to detect any significant signs e.g. presence of a sinus track/abscess related to the socket, foreign body, sequestrum, oroantral fistula, erythematous swelling around the socket, or an exophytic growth extruding from the socket
4. Radiographic investigation: severe bone destruction viewed on periapical radiographs should not be assessed in isolation, but in the context of the rest of the mouth by utilizing other radiographic views such as OPG
5. Curettage of the socket and the specimen should be sent for histologic examination (this service may not be available at primary dental care setting in the UK)
6. Patients with no signs of proper healing after 4 weeks should be referred to a specialist care – 2 weeks urgent referral in case of suspicion of malignancy. The patient should be informed of reason for their referral, and provided with a copy of the referral letter or *pro forma*

Table 3: Description of the diseases associated with non-healing extraction socket in this study (in no particular order)

Disease	Definition	Epidemiology	Potential Oral Manifestations
Ameloblastoma [29,30]	• It is an uncommon, slowly-growing, locally invasive odontogenic tumour characterized by expansion and a tendency for local recurrence if not adequately treated • The tumour is classified by the 2017 WHO Classifications of Head and Neck Tumours into: conventional (75-86% of all cases), unicystic (13-21% of cases) and extraosseous/ peripheral (1-4% of all cases)	• It is rare; with estimated annual incidence of only 0.1 cases per million population • It is, however, the most common odontogenic tumour excluding odontomas • The peak incidence of diagnosis is in the 4th and 5th decades of life, but the age range is wide: 8-92 years • It has no sex predilection • Approximately 80-85% of ameloblastoma arise in the mandible, predominantly the posterior region, and 10-15% in the maxilla, mainly in the posterior region	• The tumour is frequently asymptomatic, and smaller lesions may only be detected accidentally during a routine radiographic examination • Early presentation is often typically of an asymptomatic, slowly-growing swelling or jaw expansion, often involving the buccal and lingual cortical plates • If untreated, the tumour may undergo an accelerated growth resulting in marked complications such as malocclusion, paraesthesia, facial deformity, and limited mouth opening • The tumour can reach a huge size and can be fatal • The typical radiographic appearance is of a multilocular (bubble soap or honeycomb) appearance, frequently with buccal and lingual expansion and root resorption is common • Ameloblastoma may also appear as a unilocular radiolucency
Sarcoidosis [31,32]	It is a chronic inflammatory granulomatous disease of unknown aetiology, commonly affecting the lungs and lymph nodes, but any organ can be involved	• It is estimated that around 1 in every 10,000 people have sarcoidosis in the UK • Sarcoidosis is prevalent in both men and women as well as all major ethnicities with a slight female predilection	• Orofacial presentations are rare • If sarcoidosis involves soft tissues of the oral cavity, it may present as a localized, firm swelling affecting the lips, gingivae, floor of mouth, tongue, hard or soft palate, buccal mucosa and vestibule • If it involves the jaws it may manifest as loosening of teeth or non-healing extraction socket

			• Sarcoidosis of salivary glands may present as a swelling of the parotid or submandibular glands, and xerostomia
Plasmacytoma [33,34]	• It is an uncommon, localized neoplastic proliferation of monoclonal plasma cells that usually arises within bone • It may arise as solitary bone lesions (solitary plasmacytoma of bone or SBP), or infrequently as soft-tissue lesions (extramedullary plasmacytoma).	• The average age at diagnosis of plasmacytoma is 55 years with a male-to-female ratio of approximately 2:1 • SBP most commonly affects the spine. It very rarely involves maxillofacial region where it may affect the skull and jaw bones - the mandible is involved in only 4.4% cases of SBP • Extramedullary plasmacytomas may affect in the head and neck region: lesions have been reported in the tonsils, nasopharynx, paranasal sinuses, nose, parotid glands	• The initial symptoms are often nonspecific such as swelling or bone pain, thus only detected on routine radiographic examination. However, SBP of the jaw may present as a localized lesion associated with pain, bone destruction, and pathological fractures. • Extramedullary plasmacytoma may present as an indistinctive, well-circumscribed, painless soft tissue mass
Malignant melanoma [35–37]	It is a rare malignant tumour of melanocytes	• Melanoma skin cancer is the 5th most common cancer in the UK, accounting for 5% of all new cancer cases • More than a quarter (29%) of all new melanoma skin cancer cases in the UK are diagnosed in people aged 75 and over - incidence rates are highest are highest in people aged 85 to 89	• Oral melanomas may arise as new lesions from apparently normal mucosa, but about 30–50% are preceded by oral pigmentations for several months or even years • Lesions are initially asymptomatic, and may appear uniformly brown or black, but sometimes may show other colour variations, with black, brown, grey, purple and red shades, or depigmentation • Lesions may have a smooth surface or may be ulcerated.

		• It has a very slight male predilection • Oral malignant melanoma is extremely rare. Only about 2% of all melanomas arise in the oral mucosa and these account for 0.5% of all oral malignancies • The most frequently affected oral sites are the palate and the gingiva	• Other presentations of oral malignant melanoma include bleeding, ill-fitting dentures, pain, increased mobility of teeth and non-healing of extraction sockets
Carcinoma cuniculatum (CC) [38,39]	It is a rare variant of squamous cell carcinoma (SCC) characterized by minimal cytologic atypia and a unique deeply infiltrative growth pattern resembling rabbit burrows (cuniculi)	• It primarily affects adults in the sixth and seventh decades • More than 90% of CC cases occur in the foot • CC accounts for approximately 2.7% of all oral SCC cases • It may affect the palate, tongue, alveolar mucosa, gingiva or floor of the mouth	• It often follows a slow, insidious, nonspecific course (pain, swelling, ulceration, a nodular or keratotic patch) which may resemble other benign, reactive or inflammatory disorders such as stomatitis, lichen planus or hyperplasia • Its clinical presentation is variable, frequently leads to misdiagnosis
Brown tumour of hyperparathyroidism [40–42]	It encompasses bone lesions that occur late in primary or tertiary hyperparathyroidism as a result of abnormal bone metabolism	• Brown tumours can affect one or more bones - the most commonly affected bones are the ribs, clavicles, and pelvis • Craniofacial involvement occurs in approximately 4% of cases, mainly affecting the posterior mandible	• Clinically - the tumour may present as painful, slowly-growing swelling that can reach large dimensions. It is hard on palpation, fixed to the underlying tissues, and has a significant tendency to bleed • Radiographically - it often appears as a well-defined unilocular or multilocular radiolucent lesion which may be associated with root resorption, tooth displacement, or the absence of the lamina dura

Hodgkin Lymphoma (HL) [29,43]	It is a malignant neoplasia of B-lymphocytes which arises predominantly in lymph nodes (>90)	• HL is rare. It is not among the 20 most common cancers in the UK, accounting for less than 1% of all new cancers in the UK • Hodgkin's lymphoma occurs over a wide age spectrum, with two peaks between 15 and 35 years of age, and beyond 55 years of age. • It has a slight male predilection and incidence rates are higher in the Asian and Black ethnic groups	• The classic presentation a persistently enlarging, painless, discrete mass or masses in one lymph node region, commonly the cervical and supraclavicular nodes. It rarely involves extranodal tissues (only 1-4%) • Oral involvement is rare, but may present as tonsillar enlargement, usually unilateral
Non-Hodgkin Lymphoma (NHL) [29,44]	It is a malignant neoplasia of the lymphoid tissue. The majority arise from B lymphocytes, but can also develop from T lymphocytes or natural killer cells	• NHL is more common than HL, comprising almost 90% of all diagnosed lymphomas • It is the 7th most common cancer in the UK, accounting for 4% of all new cancer cases • More than a third (36%) of all new NHL cases in the UK are diagnosed in people aged 75 and over and the incidence is highest in people aged 80 to 84	• Up to 40% of all NHLs arise at extranodal sites, most commonly the gastrointestinal tract • Oral manifestations of NHLs are variable, and often uncharacteristic which render diagnosis challenging as these findings frequently overlap with the clinical features of various diseases, these may include: 1. A solitary mass, which may become ulcerated, frequently affecting the palate or gingivae 2. Salivary gland enlargement, especially of the parotid glands 3. Painful expansive lesions of the jaw resulting in facial asymmetry, tooth mobility, displacement of teeth, which radiographically appear as bone resorption or osteolytic lesions 4. Involvement of the mandible may also lead to paraesthesia or anaesthesia in the mandible region, chin and/or lips, as well as pathological fractures

Osteomyelitis [29,45]	• It is an acute or chronic inflammatory condition of the bone, which begins as an infection of the medullary spaces, rapidly involves the haversian systems, and extends to involve the periosteum of the affected area	• It is more common in mandible than maxilla • It predominantly affects debilitated, immunosuppressed or medically compromised patients	• Presentation may include deep-seated bone pain, swelling and erythema of overlying tissues, lymphadenopathy, fever, paraesthesia of the inferior alveolar nerve, trismus, malaise, and fistulas
Langerhans cell histiocytosis (LCH) [29,46]	• It encompasses conditions characterized by aberrant and differentiation or proliferation of cells of the mononuclear phagocyte system. • Langerhans cells are dendritic, mononuclear, antigen-presenting cells normally found in the epidermis, mucosa, lymph nodes, and bone marrow	• LCH is a rare disease that is more commonly seen in children but is increasingly recognised in adults. There are about 50 new cases in the UK each year • It affects 4-8 children and 1-2 adults per million each year • About 10% of LCH cases show involvement of the jaws, and the mandible is affected in nearly 75% of the cases, either alone or in polyostotic disease	• Loss of clinical attachment and tooth mobility • Often appear radiographically as a well-defined 'punched out' radiolucent lesion • Tooth showed progressive horizontal loss which became extensive that may appear as floating in air
Maxillary sinus tumour [10,47–49]	• Primitive neuroectodermal tumour (PNET) is a rare, highly malignant neoplasia with poor prognosis that belongs to Ewing's sarcomas • Inverted papilloma (IP) is an uncommon benign tumour of nasal cavity and paranasal sinuses that is locally invasive and has tendency for recurrence and malignant transformation	• PNET accounts for 1-4% of all soft tissue neoplasms, but it is extremely rare in the head and neck region. It predominantly affects children and young adults • IP accounts 0.5–4% of all sinonasal tumors. The maxillary sinus is the most common site for. It mainly affects males at 50-60 years of age	• PNET is extremely rare in the oral cavity but may present as nonspecific pain over posterior maxilla, looseness of maxillary molars, enlargement of maxilla or extraction socket non-healing • IP may present as a palatal swelling, facial pain, facial asymmetry or a non-healing extraction socket

Table 4: Preoperative features that may be suggestive of increased risk of later extraction socket non-healing (*)

History	1. History of cancer 2. History of radiotherapy to the head and neck 3. History of anti-resorptive or antiangiogenetic therapy 4. History of immunosuppression 5. Sudden looseness of teeth without history of trauma, or recent dental treatment 6. Sudden onset of numbness of the lip or chin with no history of recent trauma or fracture to the mandible 7. Sudden onset of numbness or tingling sensation over the cheek or upper lip
Clinical Examination	1. Extremely mobile tooth/teeth with no apparent fracture or periodontal disease. This should be assessed in the context of the rest of mouth 2. Excessive bleeding on probing which cannot be stopped with local measures
Radiographic Investigation	1. Severe (often irregular) destruction of bone so that the tooth or teeth appear as being floating in air (Figure 3)[18] 2. Tooth associated with a punched-out or multilocular radiolucency not consistent with a cyst 3. Tooth/teeth associated with a poorly-defined radiolucency or mixed radiopaque/radiolucent lesion

(*) If a patient presents with one or more of these manifestations before extraction, they should be scheduled for a regular follow up following extraction on at least a weekly basis, and should be referred if no signs of healing are detected as described (2 weeks if malignancy is suspected)

Table 5: Postoperative features which suggest a potential sinister underlying cause of a non-healing socket (*)

History	1. History of cancer 2. History of radiotherapy to the head and neck 3. History of anti-resorptive or antiangiogenetic therapy 4. History of immunosuppression e.g. organ transplant patients 5. Severe deep-seated bone pain developing after an extended period (e.g. weeks) following extraction; unlike dry socket which usually develops within 2-3 days 6. Sudden numbness of the upper lip or cheek or lower lip and/or chin with no history of trauma or fracture of the mandible

Clinical examination	1. No signs of proper healing of 4 weeks (8 weeks if on anti-resorptive or antiangiogenic medication) e.g. an empty socket with visible bony walls and little (if any) soft tissue granulation 2. An intra-oral sinus track or extra-oral fistula related to the extracted tooth 3. An exophytic soft tissue lesion fungating from the socket 4. Paraesthesia of the upper lip or cheek, or lower lip and/or chin or gingiva on the side of the extracted tooth 5. Palpable or enlarged lymph nodes
Radiographic investigations	Presence of bone sequestration, extensive irregular bone loss, poorly-defined radiolucency or mixed radiopaque/radiolucent lesion related to the extracted tooth, or pathological fracture (Figure 4)[18]

(*) If a patient presents one or more of these delayed manifestations following extraction, they should be be referred as described (2 weeks if malignancy is suspected)

Box 1: Case study [50,51]

A 65-year-old female patient, who was an ex-smoker with known history of periodontal disease, presented to her dentist with a painful lower right second molar (LR7). She was diagnosed with periodontal abscess and the tooth was extracted, but 2 weeks later she returned to the surgery complaining of pain and a bad taste in the lower right quadrant. A diagnosis of an infected socket was made this time. The socket was thoroughly irrigated and the patient was prescribed a course of antibiotics. However, she continued to experience pain and discomfort in the area, while there were no signs of proper healing of the LR7 extraction socket. On one occasion, the adjacent lower right first molar LR6 was extracted, and contrary to LR7, the socket healed uneventfully this time. It took the patient's dentist 18 weeks to make a routine dental hospital referral for presumed chronic periodontal disease. However, an incisional biopsy taken later on at the hospital confirmed that the lesion was squamous cell carcinoma. The patient underwent extensive surgery followed by facial reconstruction and radiotherapy. A solicitor acting on the behalf of the patient sent a claim letter to the surgery alleging clinical negligence in the delayed diagnosis and referral for suspected mouth cancer. Sadly, the patient succumbed to the disease and the negligence claim was settled with a substantial compensation.

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