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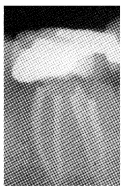

CASE REPORT

Osteomyelitis due to arsenic trioxide use for tooth devitalization

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Abstract

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Aim To present a case of osteomyelitis that was caused by the use of arsenic trioxide during root canal treatment in a mandibular left first molar.

Summary Arsenic was once in common use to devitalize inflammed pulp tissue before root canal treatment. Its prolonged application or leakage leads to toxic effects beyond the pulp tissue, and necrosis of periodontal tissues and supporting alveolar bone has been described. This report presents a case of osteomyelitis resulting from leakage of arsenic trioxide used in pulp devitalization. Sequestrectomy and excision of non-vital alveolar bone was performed to treat the severe tissue necrosis.

Key learning points

- Agents containing arsenic are still employed by some clinicians and may be encountered when patients present with tissue destruction resulting from their use.
- Dental practitioners should be aware that arsenic paste may diffuse into periodontal tissues through apical, lateral or accessory canals, through perforations and around leaking restorations.
- Osteomyelitis caused by arsenic trioxide can be treated by a combination of pharmacotherapeutic and invasive surgical methods.
- Arsenic pastes have no place in endodontic practice.

Keywords: arsenic trioxide, osteomyelitis, sequestrectomy.

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Introduction

Arsenic was used both as a therapeutic agent and as a poison in ancient Greek and Roman times (Gallagher 1998). Arsenic served for the treatment of syphilis and as a tonic in Fowler's syndrome until the introduction of Penicillin (Katzung 1989, Antman 2001).

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Today, its therapeutic use in medicine is limited to certain infectious conditions such as trypanosomiasis which involves the central nervous system (Katzung 1989). Recent publications have reported clinical trials on the use of arsenic trioxide in multiple myeloma and acute promyelocytic leukaemia (Gallagher 1998, Antman 2001). These clinical trials evaluated different forms of arsenic agents that could induce apoptosis and inhibit proliferation of drug-resistant cell lines (Porth 2005).

Arsenic is one of the 'tooth pulp devitalizing' agents used throughout dental history when anaesthesia was not available. Owing to its capacity to kill cells in surrounding tissues, the use of arsenic trioxide in vital pulpectomy has been reduced (Cruse & Bellizzi 1980). In addition, effective local anaesthesia techniques no longer necessitate their use.

Bone damage can occur as a result of contact with caustic chemicals and other protoplasmic poisons (Cruse & Bellizzi 1980, Yakata *et al.* 1985, Smart & Barnes 1991). Osteomyelitis is an inflammatory disease of bone caused by infection. The virulence of the causative microorganisms is an important factor for the progression and development of osteomyelitis. The hallmark of osteomyelitis is the development of sequestra which are segments of bone that have become necrotic because of the ischaemic injury caused by the inflammatory process (Lee 2004).

This report presents a case of severe bone necrosis complicated further by a superimposed pyogenic infection, osteomyelitis, resulting from arsenic trioxide use in a mandibular left first molar pulp devitalization procedure.

Case report

A 15-year-old female with severe pain, denuded mandibular bone and chronic halitosis was referred by a private practitioner to Marmara University's School of Dentistry. The history revealed that she had attended her dentist with severe pain and that endodontic treatment had been initiated immediately on tooth 36 (FDI). She was informed that 'a pulp-necrotizing agent' had been applied and a second visit would be necessary on the following day. However, she did not attend the second session because her pain had been relieved by the initial treatment.

The referring general dental practitioner stated that arsenic devitalization was his choice of treatment since local anaesthesia was ineffective. The patient experienced a throbbing pain within 6 days of the arsenic trioxide application and went back to the dentist. Tooth 36 was extracted and a combination of oral amoxicillin trihydrate 825 mg and potassium clavilanate 125 mg was prescribed twice a day over a 5 day period. The practitioner subsequently noticed the denudation of bone and referred the patient to a university clinic.

On presentation, the patient had pyrexia (38.5 °C) and general fatigue. Extraoral clinical examination revealed facial asymmetry with swelling of the mandibular body on the left side associated with painful submandibular lymphadenopathy. Intraorally, the oral hygiene was poor and electrical pulp sensitivity tests of teeth 35 and 37 were negative. These teeth had mobility grade of II. Loss of alveolar mucosa and exposed necrotic alveolar bone was observed around the extraction socket (Fig. 1). Severe halitosis, and the presence of sequestrum were the principal symptoms leading to the clinical diagnosis of osteomyelitis.

Panoramic and periapical radiographs revealed a well-defined radiolucent demarcation line between the surrounding trabecular pattern of the teeth 34–37 and the alveolar socket of the extracted 36. Focal zones of opacification were surrounded with distinct margins (Fig. 2).

Parenteral clindamycin phosphate 600 mg was prescribed twice daily for 5 days. The patient was then given oral clindamycin hydrochloride 150 mg to be taken four times daily

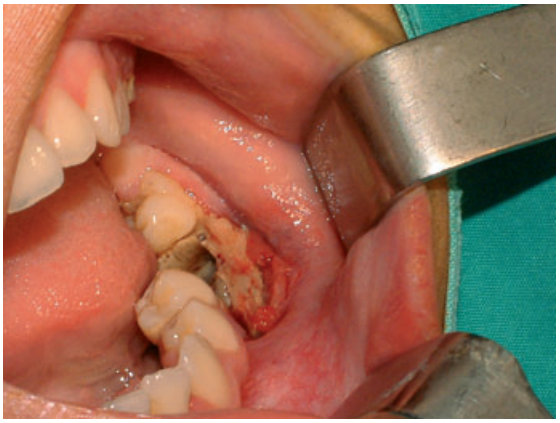

Figure 1 Intraoral view of the sequestra in the region of tooth 36.

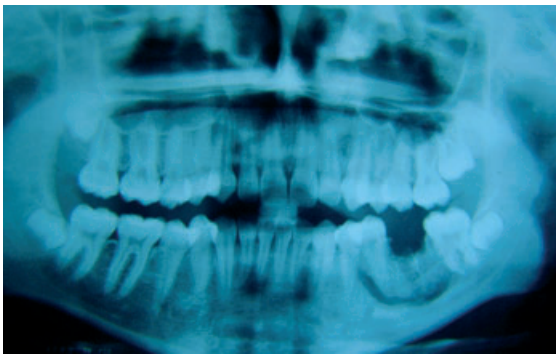

Figure 2 Panoramic radiograph showing the demarcation line between teeth 34 and 37.

for 2 weeks by the Department of Oral Surgery. Surgical intervention including the extraction of 35 and 37, sequestrectomy and excision of the nonvital alveolar bone was conducted under intravenous sedation (0.03 mg kg^{-1}; Midazolam, Roche Pharmaceuticals, Istanbul, Turkey) and local anaesthesia (40 mg ml^{-1}; Articaine HCl, Aventis Pharma, Istanbul, Turkey) (Fig. 3). An autogeneous bone graft was harvested from the rim of the piriform aperture and repositioned to the distal root surface of the tooth 34 to facilitate fixation. The surgical site was closed primarily.

Histopathological examination of the excavated material showed the diagnostic features of osteomyelitis as necrotic bone adjacent to the acute and chronic inflammatory areas. Necrotic residue of bone marrow, patchy infiltration of polymorphonuclear leukocytes, reactive fibrotic tissue in the bone marrow area including lymphocytic infiltration and areas of osteclastic resorption were examined. Reversal lines showing the waves of deposition and resorption were observed in the surrounding mandibular bone (Figs 4 and 5).

Discussion

Arsenic and its compounds can be highly toxic and even carcinogenic in cases of contact with hard or soft tissue (http://www.atsdr.cdc.gov/tfacts2.html). They have the potential to cause reactions in exposed tissues, which can lead to hypersensitivity.

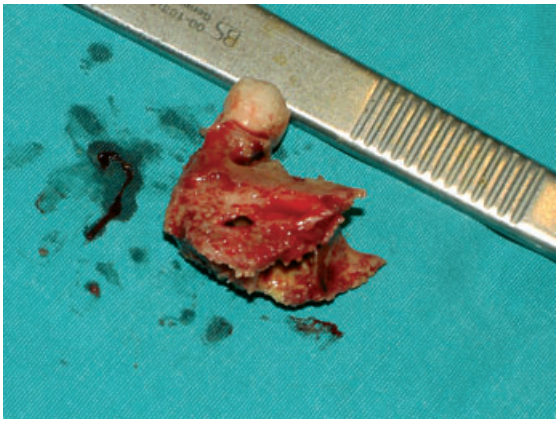

Figure 3 Sequestrectomy and extraction of teeth 35 and 37.

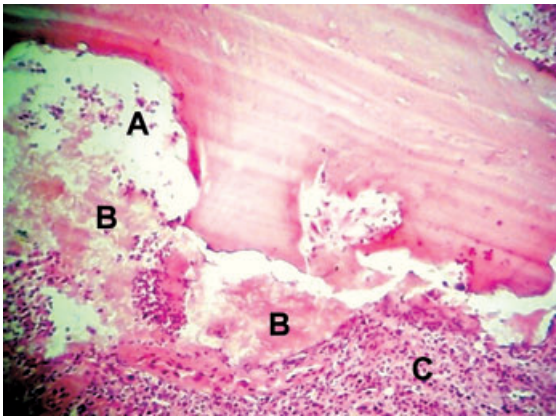

Figure 4 Photomicroscopy showing osteoclastic resorption of bone (A), necrotic remnants of bone marrow (B) and fibrotic reaction including lymphocytic infiltration (C) (haemotoxylin and eosin, original magnification, 40×).

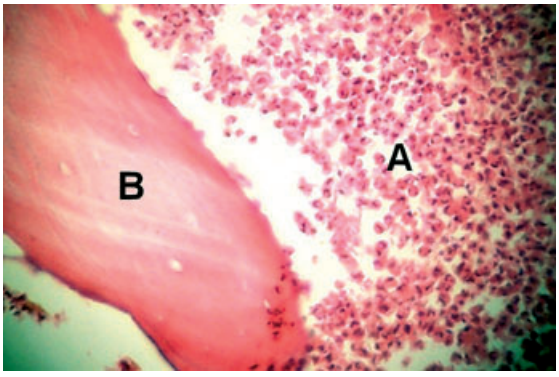

Figure 5 Photomicroscopy revealing the infiltration of the bone marrow (A) by polymorphonuclear leukocytes due to superimposed pyogenic infection adjacent to the trabecule of the bone (B) (haemotoxylin and eosin, original magnification, 40×).

Arsenic intoxication can result from ingesting contaminated water, food or soil, breathing contaminated sawdust, workplace air or smoke from arsenic-preserved wood (Chakraborti & Saha 1987, Agency for Toxic Substances and Disease Registry. Arsenic, 2005:

http://www.atsdr.cdc.gov/tfacts2.html). Arsenic poisoning is a serious public health problem in many parts of the world, where it predisposes people to a variety of diseases, including skin, bladder, lung and liver cancers (Gallagher 1998, Agency for Toxic Substances and Disease Registry. Arsenic, 2005: http://www.atsdr.cdc.gov/tfacts2.html). Arsenic absorption through the skin is due to lipid solubility and when this occurs it is followed by an adverse dermatological reaction known as arsenical dermatosis (Chakraborti & Saha 1987). Arsenical dermatosis can appear as contact dermatitis, ulcerations, hyperkeratotic reactions, hyperpigmentation, hypopigmentation, pyoderma, epitheliomas and folliculitis. In addition, arsenical dermatosis can trigger Stevens-Johnson Syndrome (Chakraborti & Saha 1987, Milton & Rahman 1999, Porth 2005).

Major toxicological effects of inorganic arsenic compounds are caused by the trivalent form of arsenic that is more lipid-soluble than the pentavalent form. The trivalent form of arsenic inhibits sulphydril enzymes and is highly destructive to the epithelial lining of the respiratory and gastrointestinal tracts as well as skin and mucous membranes. Arsenic compounds replace the inorganic phosphorous during synthesis of high-energy phosphates so that the uncoupling of oxidative phosphorylation results in impaired cellular metabolism. As an occupational hazard this may be manifested as altered DNA methylation, oxidative stress, altered cell proliferation, cocarcinogenesis and genotoxicity (Katzung 1989, Porth 2005).

Arsenic is usually employed in dentistry as a water-soluble compound: arsenic trioxide (As_2O_4) forming arsenious acid (H_3AsO_4). Clinicians should know that it does not remain within the root canals but may also diffuse to the surrounding periodontal tissues through apical, lateral or accessory canals, and can lead to periapical tissue sensitivity due to its cytotoxicity and associated biological effects (Cruse & Bellizzi 1980, Yakata *et al.* 1985, Smart & Barnes 1991). In addition, prolonged application and/or leakage of arsenic trioxide can lead to necrosis of oral tissues and osteomyelitis or oroantral fistulas (Yakata *et al.* 1985, Smart & Barnes 1991, Bataineh *et al.* 1997, Ozmeric 2002, Yalcin *et al.* 2003, Garip *et al.* 2004).

Arsenic agents are still available to clinicians even though their use is contraindicated and despite numerous publications reporting complications following their use. Yakata *et al.* (1985) presented a case of extensive bone destruction in the mandibular ramus following pulp devitalization with arsenic trioxide. Yalcin *et al.* (2003) reported a case of bilateral oroantral fistulas as a result of arsenical paste leakage from the pulp chamber of teeth to the surrounding tissue. Garip *et al.* (2004) also described the management of arsenic trioxide necrosis in the maxilla in two cases.

Destruction of bone associated with osteomyelitis usually requires extraction of related teeth. In this case, involved teeth were extracted due to extensive bone necrosis and sequestrum formation.

Conclusions

- Some dentists continue to use arsenicals in their endodontic practice.
- All dentists should be alert to the effects of such agents and consider them in the differential diagnosis should a patient attend with severe tissue damage.
- There is no indication for the use arsenic agents in modern dental practice because more effective, contemporary local anaesthetic agents and techniques are available.

References

Agency for Toxic Substances and Disease Registry. Arsenic. (2005) Available at http://www.atsdr.cdc.gov/tfacts2.html (last updated September 2005).

Antman KH (2001) Introduction: the history of arsenic trioxide in cancer therapy. *The Oncologist* **6**, 1–2.

Bataineh AB, al-Omari MA, Owais Al (1997) Arsenical necrosis of the jaws. *International Endodontic Journal* **30**, 283–7.

Chakraborti AK, Saha KC (1987) Arsenical dermatosis from tubewell water in West Bengal. *Indian Journal of Medical Research* **85**, 326–34.

Cruse WP, Bellizzi R (1980) A historic review of endodontics. 1689–1963. Part I. *Journal of Endodontics* **6**, 495–9.

Gallagher RE (1998) Arsenic-New life for an old potion. *The New England Journal of Medicine* **339**, 1389–91.

Garip H, Salih IM, Sener C, Goker K, Garip Y (2004) Management of arsenic trioxide necrosis in the maxilla. *Journal of Endodontics* **30**, 732–6.

Katzung BG (1989) *Basic and Clinical Pharmacology*, 4th edn. Connecticut, CT: Appleton & Lange, pp. 745–7.

Lee L (2004) Inflammatory lesions of the jaws. In: White SC, Pharoah MJ (eds) *Oral Radiology: Principles and Interpretation*, 5th edn. St Louis: Mosby, pp. 373–4.

Milton AH, Rahman M (1999) Enviromental pollution and skin involvement pattern of chronic arsenicosis in Bangladesh. *Journal of Occupational Health* **41**, 207–8.

Ozmeric N (2002) Localized alveolar bone necrosis following the use of an arsenical paste: a case report. *International Endodontic Journal* **35**, 295–9.

Porth CM (2005) *Pathophysiology: Concepts of Altered Health States*, 7th edn. Philadelphia, PA: Lippincott Williams & Wilkins, pp. 331, 335, 1481.

Smart ER, Barnes IE (1991) Tissue necrosis after using an arsenical endodontic preparation. A case report. *International Endodontic Journal* **24**, 264–9.

Yakata H, Azumi T, Kawasaki T, Nakajima T (1985) Extensive osteolysis of the mandible following devitalization of a tooth by arsenic trioxide. *Journal of Oral and Maxillofacial Surgery* **43**, 462–6.

Yalcin S, Aybar B, Haznedaroglu F, Yucel E (2003) Bilateral oroantral fistulas following devitalization of teeth by arsenic trioxide: a case report. *Journal of Endodontics* **29**, 205–7.

