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Case Report

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Persistent pain after successful endodontic treatment in a patient with Wegener's granulomatosis: a case report

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ABSTRACT

Wegener's granulomatosis (WG) is a condition with immune-mediated pathogenesis that can present oral manifestations. This report describes the case of a patient diagnosed with WG 14 years previously, who was affected by persistent pain of non-odontogenic origin after successful endodontic treatment. A 39-year-old woman with WG was diagnosed with pulp necrosis and apical periodontitis of teeth #31, #32, and #41, after evaluation through a clinical examination and cone-beam computed tomography (CBCT). At the first appointment, these teeth were subjected to conventional endodontic treatment. At 6- and 12-month follow-up visits, the patient complained of persistent pain associated with the endodontically treated teeth (mainly in tooth #31), despite complete remission of the periapical lesions shown by radiographic and CBCT exams proving the effectiveness of the endodontic treatments, thus indicating a probable diagnostic of persistent pain of non-odontogenic nature. After the surgical procedure was performed to curette the lesion and section 3 mm of the apical third of tooth #31, the histopathological analysis suggested that the painful condition was likely associated with the patient's systemic condition. Based on clinical, radiographic, and histopathological findings, this unusual case report suggests that WG may be related to non-odontogenic persistent pain after successful endodontic treatments.

Keywords: Case reports; Granulomatosis with polyangiitis; Root canal therapy; Toothache

INTRODUCTION

Apical periodontitis (AP) is a chronic inflammatory disease that affects the periapical tissues and results from the host's immune response to endodontic infection [1,2]. More than half of the worldwide adult population has at least 1 tooth affected by AP [3]. Non-surgical root canal treatment for teeth affected by pulp necrosis and AP tackles the endodontic infection by sealing the pulp cavity to allow the patient's immune system to play its role in recovering periapical tissue health [4]. The absence of clinical signs and symptoms, as well as the healing or maintenance of periapical tissue health, is the main indicator of successful

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endodontic treatment [5]. Conversely, persistent pain and the development or maintenance of periapical lesions represent strong signs of initial therapy failure, which may require reintervention [5]. Preoperative pain, previous painful dental treatments, female sex, and a history of chronic systemic disease are factors strongly associated with persistent pain after endodontic therapy [6,7].

Granulomatosis with polyangiitis, also known as Wegener's granulomatosis (WG), is a very rare, idiopathic, and multisystemic inflammatory disease, whose etiology has not yet been fully elucidated [8]. The worldwide prevalence of WG is estimated at 23.7 to 156.5 per million [8]. The pathogenesis is immune-mediated with vasculitis of small/medium caliber vessels and formation of autoantibodies, a characteristic confirmed by specific hematological findings [8]. WG lesions are marked by a triad of histopathological features: necrosis, granulomatous inflammation, and vasculitis with organ and tissue damage [9,10]. The clinical manifestations are usually limited to the upper respiratory tract, lungs, and kidneys, although WG can also affect other organs or tissues [9,10]. Oral manifestations of WG occur in approximately 6% to 13% of patients [8]. The most frequent oral manifestation is gingival hyperplasia, reported in the literature as "strawberry gingivitis" [11,12]. However, other sites can also be involved, such as the palate, salivary glands, bone tissue, and teeth [8].

Nervous system involvement can occur in 21% to 45% of patients with WG, with peripheral nerve injuries being the most common manifestation [8]. When pain cannot be attributed to any pathological process, neuropathic mechanisms should be suspected [13]. To date, there is no report in the literature of persistent dental pain associated with WG. Therefore, this paper presents the case of a female patient diagnosed with WG who experienced persistent pain in the lower left central incisor after endodontic treatment with complete periapical healing.

CASE REPORT

A 39-year-old Caucasian female patient, who had been diagnosed with WG 14 years previously, was referred for endodontic treatment of her left mandibular central incisor (tooth #31) following an emergency visit. She reported no history of trauma, dental caries, or previous dental procedures. During the anamnesis, the patient reported taking rituximab (500 mg) every 6 months to control the progression of WG. An extraoral examination did not reveal swelling, sinus tracts, regional lymphadenopathy, or temporomandibular disorders. An intraoral examination revealed a tooth with a provisional seal in the lingual surface, probing depth within normal limits, and no pathological tooth mobility. It also indicated mild discomfort in response to vertical and horizontal percussion and a negative result of the cold pulp test (EndoIce, Coltene/Whaledent Inc., Cuyahoga Falls, OH, USA). Despite light incisal wear on the mandibular incisors, no significant occlusal dysfunction or other significant clinical changes were identified in the adjacent teeth. However, the left lateral (tooth #32) and the right central (tooth #41) mandibular incisors also responded negatively to the pulp sensibility tests. Radiographically, tooth #31 showed an apical radiolucency, and both teeth #32 and #41 showed a small thickening of the apical periodontal ligament space (**Figure 1A**). An immediate request for cone-beam computed tomography (CBCT) was made to complement the diagnosis, which showed that the apical lesion extended to the 3 abovementioned mandibular incisors (**Figure 1B and 1C**). Considering the clinical and radiographic findings, the teeth were diagnosed with pulp necrosis, and endodontic treatment was proposed. The patient completed an informed consent form for the intervention.

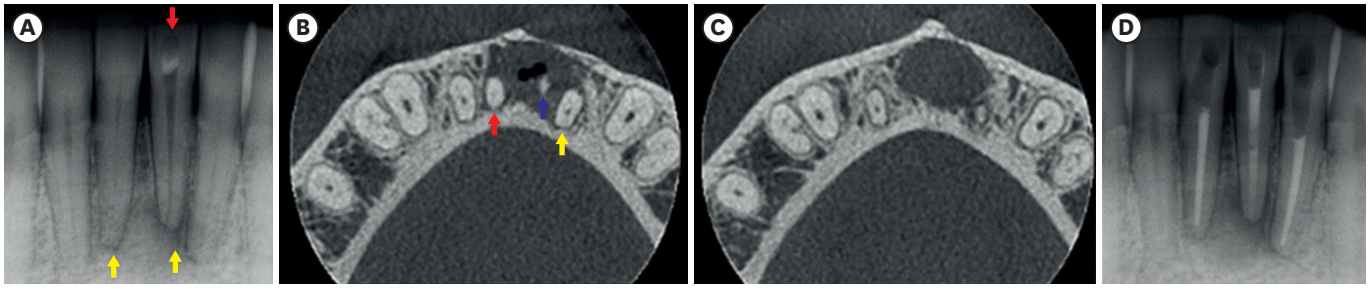

Figure 1. Images referring to the first phase of the treatment (diagnosis and completion of the endodontic interventions). (A) Initial periapical radiography. Red arrow: tooth #31 with previous root canal access and periapical lesion. Yellow arrows: teeth #32 and #41 with apical periodontal ligament space thickening. (B and C) Initial cone-beam computed tomography images (axial view). Large periradicular lesion affecting the anterior region of the mandible and the root apices of teeth #31 (blue arrow), #32 (yellow arrow), and #41 (red arrow). (D) Final periapical radiography, with teeth #32 and #41 filled with gutta-percha and endodontic sealer, and tooth #31 filled with mineral trioxide aggregate.

Local anesthesia (1.8 mL of 2% lidocaine with 1:80,000 epinephrine; DFL, Taquara, RJ, Brazil) was administered, and the teeth were isolated with a rubber dam. The operating field was disinfected with 2.5% sodium hypochlorite (NaOCl). Initial removal of the temporary seal (tooth #31) and coronary access (teeth #32 and #41) were achieved with a high-speed diamond bur (#1014 and #3083; KG Sorensen, Cotia, SP, Brazil). Initial exploration of the root canals was performed with a size 15 K-file (Dentsply-Maillefer, Tulsa, OK, USA), and the cervical and middle thirds were prepared with ProFile Orifice Shapers (Dentsply-Maillefer) under copious irrigation with 2.5% NaOCl. The root canals were measured with an electronic apex locator (Root ZX II; J Morita, Kyoto, Japan), and the working lengths (WLs) were established at 1 mm short of the "apical foramen". The anatomical diameters of the canals were matched with a size 25 K-file for tooth #31 and a size 20 K-file for teeth #32 and #41. The ProFile system (Dentsply-Maillefer) was used to perform the chemomechanical preparations, as per the manufacturer's recommendations. The respective final files used for teeth #31, #32 and #41 were size 45/0.04, 45/0.04 and 40/0.04. During the cleaning and shaping process, the canals were irrigated with 2.5 mL of 2.5% NaOCl after each use or change of file, by using a NaviTip 30-G tip (Ultradent Products, South Jordan, UT, USA) coupled to a 5-mL syringe, followed by apical patency with a size 15 K-file inserted up to the apical foramen. The final irrigation was carried out with 3 mL of 17% ethylenediaminetetraacetic acid solution followed by 3 mL of 2.5% NaOCl. The root canals were then dried with sterile absorbent paper points (Dentsply-Maillfer).

The root canal was filled with mineral trioxide aggregate (Angelus, Londrina, PR, Brazil) to guard against apical root resorption and possible overextension of tooth #31. Teeth #32 and #41 were obturated with AH Plus sealer (Dentsply Sirona, Tulsa, OK, USA) and gutta-percha cones (Dentsply-Maillefer). First, the gutta-percha cones were fitted with a "tugback" at the WL. They were then coated with AH Plus sealer and inserted into the root canals. The filling material was thermoplasticized using a #45 McSpadden condenser (Dentsply-Maillefer) activated in a clockwise direction, until it reached 5 mm above the WL. Next, vertical compaction was performed with a gutta-percha condenser (Odous de Deus, Belo Horizonte, MG, Brazil), and the excess gutta-percha was removed up to 1 mm below the cementoenamel junction. Next, the access cavities were sealed using a glass ionomer cement (S.S. White, Rio de Janeiro, RJ, Brazil). The final periapical radiograph was performed after checking the functional occlusion of the teeth (**Figure 1D**), and the patient was referred to her general dentist for permanent coronal restorations.

At the 6-month follow-up visit, the patient complained of persistent symptoms in the same region. No important abnormalities were observed in the intraoral examination or clinical

tests. Periapical radiographs revealed a healed apical area around the endodontically treated teeth (**Figure 2A**). A new CBCT examination was requested to investigate the source of the patient's reported discomfort, which confirmed that the apical area was in the process of healing (**Figure 2B-2G**).

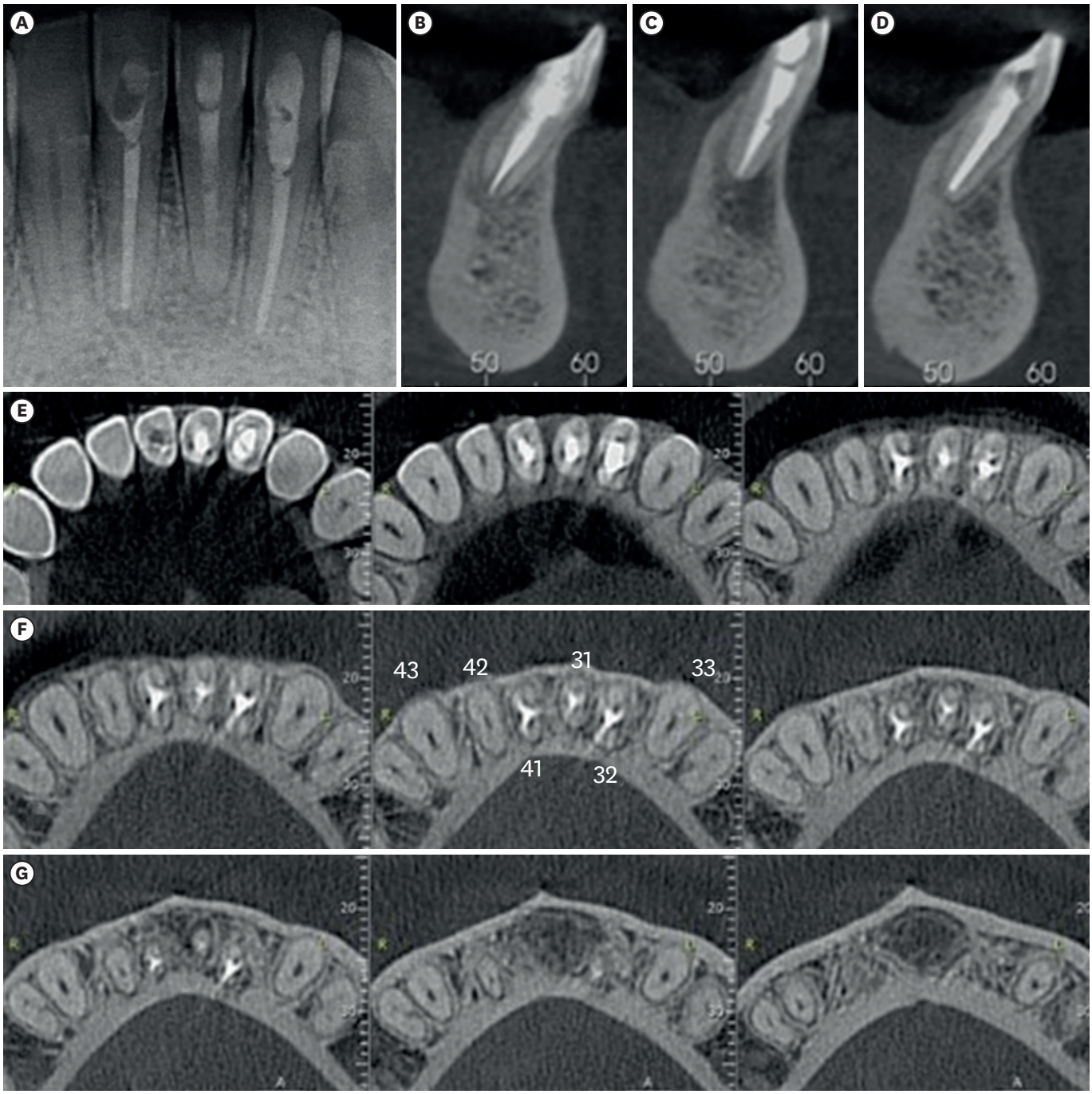

Figure 2. Images referring to the first follow-up. (A) 6-month follow-up radiography. (B and D) Cone-beam computed tomography (CBCT) images (sagittal views) of teeth (B) #32, (C) #31 and (D) #41 with evidence of the apical repair process. (E-G) CBCT images (axial views), (E) cervical, (F) middle, and (G) apical sections with evidence of the apical repair process and decreased lesion size.

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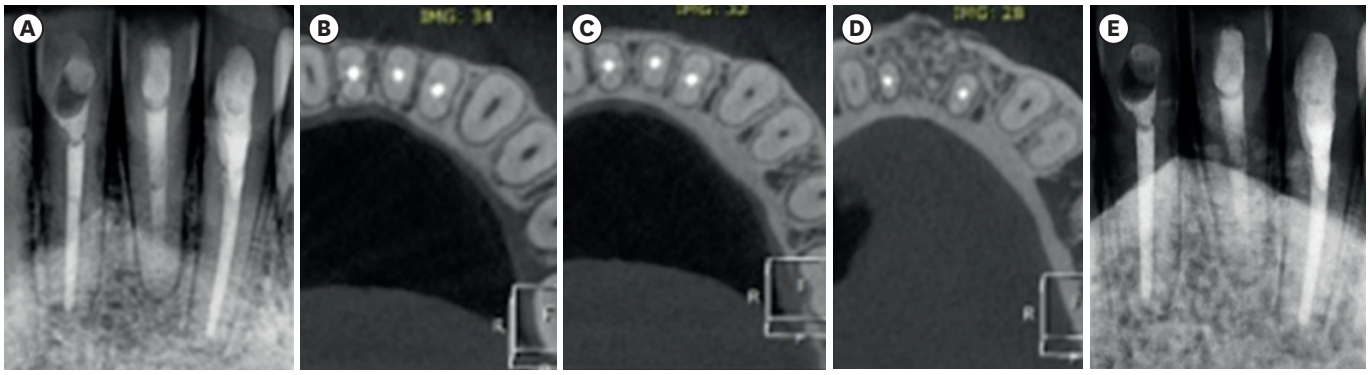

Figure 3. Images referring to the second follow-up (A-D), and 1 month after the surgical procedure (E). (A) 12-month follow-up radiograph indicating complete apical repair. (B-D) Cone-beam computed tomography images **(**axial views), (B) cervical, (C) middle, and (D) apical sections with evidence of complete apical repair and total remission of the lesion. (E) Periapical radiograph 1 month following apical surgery.

When the patient presented for a 12-month follow-up appointment, she reported important symptoms related to the same region—moderate pain and episodes of edema since the last visit. All clinical tests were repeated, and no abnormalities were identified in teeth #32 or #41. However, tooth #31 had moderate pain on vertical percussion. Periapical radiographs revealed a completely healed apical area around the group of endodontically treated teeth (**Figure 3A**). A new CBCT examination was requested, which confirmed that the healing process was complete (**Figure 3B-3D**). At this time, the clinical signs and symptoms reported by the patient, together with the results of the imaging examinations, supported the likely diagnosis—success of the recent endodontic therapy and atypical dental pain in tooth #31.

Apical surgery was proposed to allow the histopathological analysis of the region. The patient agreed and signed an informed consent form. Local anesthesia was performed (1.8 mL of 4% articaine with epinephrine 1:100,000 [DFL]), a full-thickness, sub-marginal incision was made, and the flap was raised to expose the area corresponding to the apex of tooth #31. Next, an osteotomy was conducted to expose the root apex by using a size 170 bur (KG Sorensen). Local tissue was removed with periodontal curettes for sending to the histopathological examination, followed by resection of 3mm of the apical portion of the root with a Zekrya bur (Dentsply-Maillefer) under constant irrigation with saline solution. After, the radicular apical surface was carefully analyzed, and no signs of cracks or fractures were observed. The bone cavity was filled with an allogeneic graft, and the flap was repositioned and sutured (Vicryl 4.0; Ethicon, Somerville, NJ, USA). At the 1-month follow-up appointment, the patient reported no further symptoms related to tooth #31. Clinical examination revealed no pain on percussion or palpation. A radiographic examination revealed no alterations in the periapical tissues (**Figure 3E**). The same was observed at the 6-, 12-, and 24-month follow-up visits, proving the success of the surgical procedure.

The histopathological analysis showed a well-organized fibrous connective tissue presenting a mild perivascular inflammatory infiltrate (**Figure 4A**), vascular congestion (**Figure 4B**), and blood vessels with vasculitis-characterized wall thickening (**Figure 4C**).

DISCUSSION

The clinician should take into account clinical, radiographic, and histological parameters to evaluate the success of endodontic therapy. Although histological analyses are considered

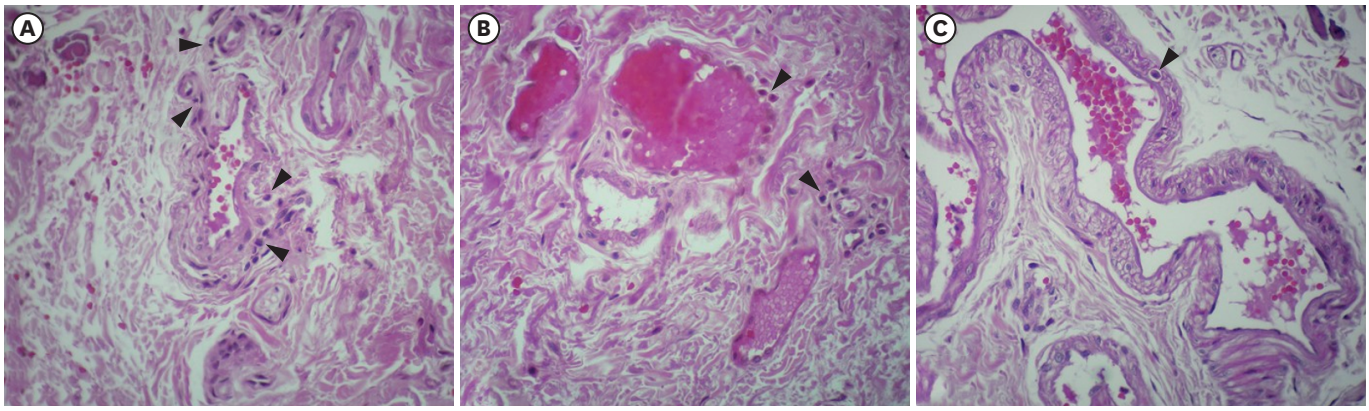

Figure 4. Histopathological analysis (hematoxylin and eosin, ×400). (A) Well-organized fibrous connective tissue with mild perivascular inflammatory infiltrate. (B) Congested blood vessels. (C) Blood vessels with wall thickening. Arrowheads: inflammatory cells.

the "gold standard" to assess healing processes in general, they are not performed frequently because they are only possible after a surgical procedure is performed [14,15]. In the case report presented herein, the CBCT exam indicated the success of initial endodontic therapies, marked by the absence of inflammation and complete healing of periapical tissues. However, persistent postoperative pain required endodontic reintervention, thus calling for histological analysis. Other studies have also presented discordant results based on the clinical, radiographic, and histological parameters used to evaluate the success of endodontic therapy. Brynolf [16] demonstrated that almost all endodontically treated teeth showed some degree of histologically evidenced periapical inflammation, despite the success from a radiographic perspective. Ricucci *et al.* [17] evaluated the outcomes of successful clinical and radiographic endodontic interventions histologically and observed inflammatory processes ranging from moderate to intense in the apical connective tissue of endodontically treated teeth.

The persistence of clinical signs and symptoms, as well as the development or maintenance of periapical lesions, are indicative signs of endodontic therapy failure [5]. Persistent pain after endodontic treatment usually occurs due to the permanence of periapical disease [18,19]. However, persistent pain in cases of periapical healing may be associated with other causes, which have an average frequency of 5% to 17% [6,20-22]. Significant predictive factors of the persistence of pain after endodontic therapy include preoperative tooth pain (particularly lasting over 3 months), a previous painful dental intervention, diseases marked by systemic chronic pain, and the female sex [6,7]. Some of these factors were present in the present case, such as the occurrence of persistent pain in a female patient diagnosed with WG.

Persistent pain can pose a challenge to the dentist, especially when it occurs in the absence of clinical and radiographic findings that could otherwise explain the cause of the pain. According to Nixdorf *et al.* [23], persistent pain after 6 months of endodontic treatment may be of non-odontogenic origin in at least half of the cases. Sinusitis, myofascial pain, headache, neuropathic disorders, neuralgia induced by osteonecrosis cavitation, and neoplasms are examples of conditions that can simulate symptomatic AP [23]. However, the most common type of non-odontogenic pain that can simulate odontogenic pain is caused by temporomandibular disorders [23].

Pain from temporomandibular disorders has been identified in 42% of patients with persistent pain after 6 months of endodontic treatment [23]. The subtype of the

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temporomandibular disorder most related to the pain of non-odontogenic origin is myofascial pain, which may originate from the masseter, temporalis, and lateral pterygoid muscles, or the temporal tendon [24]. Myofascial pain may be confused with dental pain, because of the referred pain mechanism [24]; the masseter and lateral pterygoid muscles are the most common origins [24]. These factors highlight the importance of the clinician knowing how to make diagnoses that can differentiate odontogenic pain from myofascial pain. The type of pain reported in the present case was investigated, but no factor associated with pain, or indicative of temporomandibular disorder was identified.

According to Philpot *et al.* [25], 5 predictive factors may be associated with persistent pain after endodontic treatments even after evidence of periapical healing: periapical healing: history of chronic pain and teeth responsive to pulp tests, associated with preoperative pain and affected by cracks or microfractures before the treatment, as well as the diameter of the preoperative radiolucency. In the present case report, 2 predictive factors seemed to be associated with the painful outcome: the size of the periapical lesion and the pain associated with the initial endodontic treatment. Preoperative pain may promote excessive stimulation of peripheral nociceptive fibers [26-28]. Once sensitized, peripheral neurons can amplify nerve impulses sent to the central nervous system [26-28]. Sensitization can be responsible for secondary hyperalgesia (pain exacerbated by stimuli that normally cause pain) and allodynia (pain to stimuli that normally do not cause pain), with a consequent prolonged postoperative period (lasting from hours to days) [29]. In medicine, strong scientific evidence points to significant differences in pain thresholds [30,31]. However, in dentistry, these scientific findings are still incipient [32-34].

It is important to discuss how and why a painful condition can be potentiated by a patient's systemic disorder. A substantial proportion (21% to 45%) of WG patients may have some degree of nervous involvement, mainly in the peripheral nervous system [8]. Nerve involvement can result in peripheral neuropathy, a clinical condition that can affect the peripheral nervous system [8,35]. Peripheral nervous involvement commonly leads to hyperalgesia, defined as increased sensitivity to painful stimuli [35]. In our case, the patient's neuropathic condition, in combination with her systemic condition, could have potentiated or caused non-odontogenic pain, since her endodontic treatment was considered satisfactory, with complete periapical healing.

Although periapical radiographs are essential for diagnosis and planning in endodontics, 2-dimensional (D) images provide limited information [36,37]. CBCT is useful in more complex cases [36,37], and is a resource that enables 3D visualization of the anatomy of the teeth and periapical bone in greater detail [36,37]. According to Pigg *et al.* [38], CBCT makes it easier to identify periapical bone destruction, and to distinguish between atypical odontalgia and symptomatic AP. In the present case report, the 3D analysis provided by CBCT was essential for establishing a differential diagnosis between dental pain or symptomatic AP and atypical pain. Overall, CBCT offers additional information for investigating persistent dental pain and is recommended to supplement the information provided by periapical radiographs [38]. 3D imaging has the potential to detect remaining sources of infection and failures of endodontic treatment, thereby establishing causes of post-treatment pain, such as untreated root canals, additional roots, perforations, or root fractures [36,37]. However, none of these alterations were identified in the present patient's CBCT images after endodontic treatment.

In the case report presented herein, the patient's clinical symptoms indicated that it was appropriate to perform a surgical reintervention to resolve the painful condition and allow a histological analysis. The patient was informed of the possibility that the procedure could fail (including persistent pain) [39,40]. However, she improved from the persistent symptomatology after the surgical intervention. This improvement was undeniably associated with several factors, such as the increase in her tolerance threshold for symptoms after she received a satisfactory explanation for their manifestation [41] and her development of coping strategies [42].

CONCLUSIONS

This is the first case study to report persistent pain associated with WG after successful endodontic treatment of a tooth with pulp necrosis, with the outcome of AP healing. Based on the principles of evidence-based clinical practice, and despite the potential methodological difficulties that will invariably be encountered, more clinical studies are needed to investigate the relationship between persistent pain after successful endodontic treatments in patients with WG.

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