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IgG4-Related Sclerosing Sialadenitis – Report of Three Cases –

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Chronic sclerosing sialadenitis, Mikulicz disease or Küttner tumor has been recently recognized as a spectrum of IgG4-related sclerosing disease. IgG4-related disease is characterized by a high serum IgG4 level and tissue infiltration of IgG4-positive plasmacytes. We report three cases of chronic sclerosing sialadenitis with variably associated systemic involvement. All patients presented with a submandibular mass or swelling, and all the resected submandibular glands showed diffuse lymphocytic infiltration, lymphoid follicles, and septal fibrosis. Two of the specimens revealed numerous IgG-positive plasma cells, most of which were IgG4-positive on immunohistochemical staining. One of them was associated with dacryoadenitis and hypophysitis. The other patient had ureterorenal lesions. Immunohistochemical study was unavailable in remaining one case, but the histologic features along with elevated IgG level and associated pancreatitis supported the diagnosis. All patients received steroid therapy postoperatively and are doing well. Salivary gland involvement in IgG4-related fibrosclerosis should be recognized in systemic medical pathology.

Key Words: Chronic sclerosing sialadenitis; IgG4-related sclerosing disease

Chronic sclerosing sialadenitis (CSS), formerly called Mikulicz disease (MD) or Küttner tumor (KT) is a relatively uncommon chronic inflammatory disorder of the salivary gland and most commonly affects the submandibular gland.[1] The etiology of this condition has been unknown for more than 120 years since it was reported by Mikulicz. Recently, combination of CSS and sclerosing diseases of other organs have been reported,[2,3] and elevated serum IgG4 levels have been reported in patients with MD.[4] Kitagawa *et al.*[5] first reported the presence of IgG4-positive plasma cells in a KT specimen. Since sclerosing diseases of many organs, including the pancreas, bile ducts and salivary glands are known to share IgG4-positive plasma cell infiltration,[5-7] and to often concur,[7-11] a unifying concept of IgG4-related sclerosing disease has been proposed.[12] The less commonly involved organs are the lacrimal gland and pituitary gland. Interestingly, about half of the 30 reported cases of IgG4-related dacryoadenitis[13] and 4 cases of hypophysitis[12,14] showed salivary gland involvement. We report three cases of CSS with variably accompanying systemic diseases including dacryoadenitis and hypophysitis.

CASE REPORTS

Case 1

A 56-year-old woman presented with bilateral submandibular swelling since last 1.5 years. She had a medical history of di-

abetes mellitus and had been treated with medications since 1998. Ultrasonography showed diffuse parenchymal heterogeneity with lobulation of both submandibular glands. Bilateral submandibular gland resection was performed and the excised salivary glands were diffusely enlarged, measuring up to 5×2.5×2.5 cm, with focal fibrosclerotic areas (Fig. 1A). The microscopic findings revealed multifocal patchy areas of lymphocytic infiltration with follicle formation and septal fibrosis (Fig. 1B). The infiltrates often involved the blood vessels and nerves and caused obliterative phlebitis-like features (Fig. 1C). Parenchymal atrophy was heterogeneous throughout the gland. Immunohistochemical stains revealed perifollicular presence of numerous IgG-positive plasma cells, most of which were positive for IgG4 (Fig. 1D). Postoperative study showed high titers of serum IgG (1,710 mg/dL; normal range, 700 to 1,600 mg/dL) and IgG4 (5.74 mg/dL; normal range, 0.06 to 1.21 g/L), but showed no autoantibodies including anti-SSA (Ro) and anti-SSB (La). Interestingly, levels of not only IgG4, but also IgG1 and IgG2 were elevated (Table 1). Additional computed tomography (CT) images showed diffuse enlargement with enhancement of both the lacrimal glands and the pituitary gland. Sjögren's syndrome was excluded on the basis of histologic and laboratory findings. Other organs, including the pancreas, were not thoroughly evaluated. The patient received oral prednisolone (5 mg/day) therapy, and the follow-up magnetic resonance imaging showed an improved state of the pituitary lesion. The

Table 1. Laboratory findings

	Case 1	Case 2	Case 3
IgG (mg/dL)	1,710 (700-1,600)	2,050	1,950
IgG1 (g/L)	9.68 (3.65-9.41)	N/A	5.33
IgG2 (g/L)	8.57 (1.65-5.45)	N/A	12.10
IgG3 (g/L)	0.94 (0.32-1.16)	N/A	0.28
IgG4 (g/L)	5.74 (0.06-1.21)	N/A	0.31

N/A, not available.

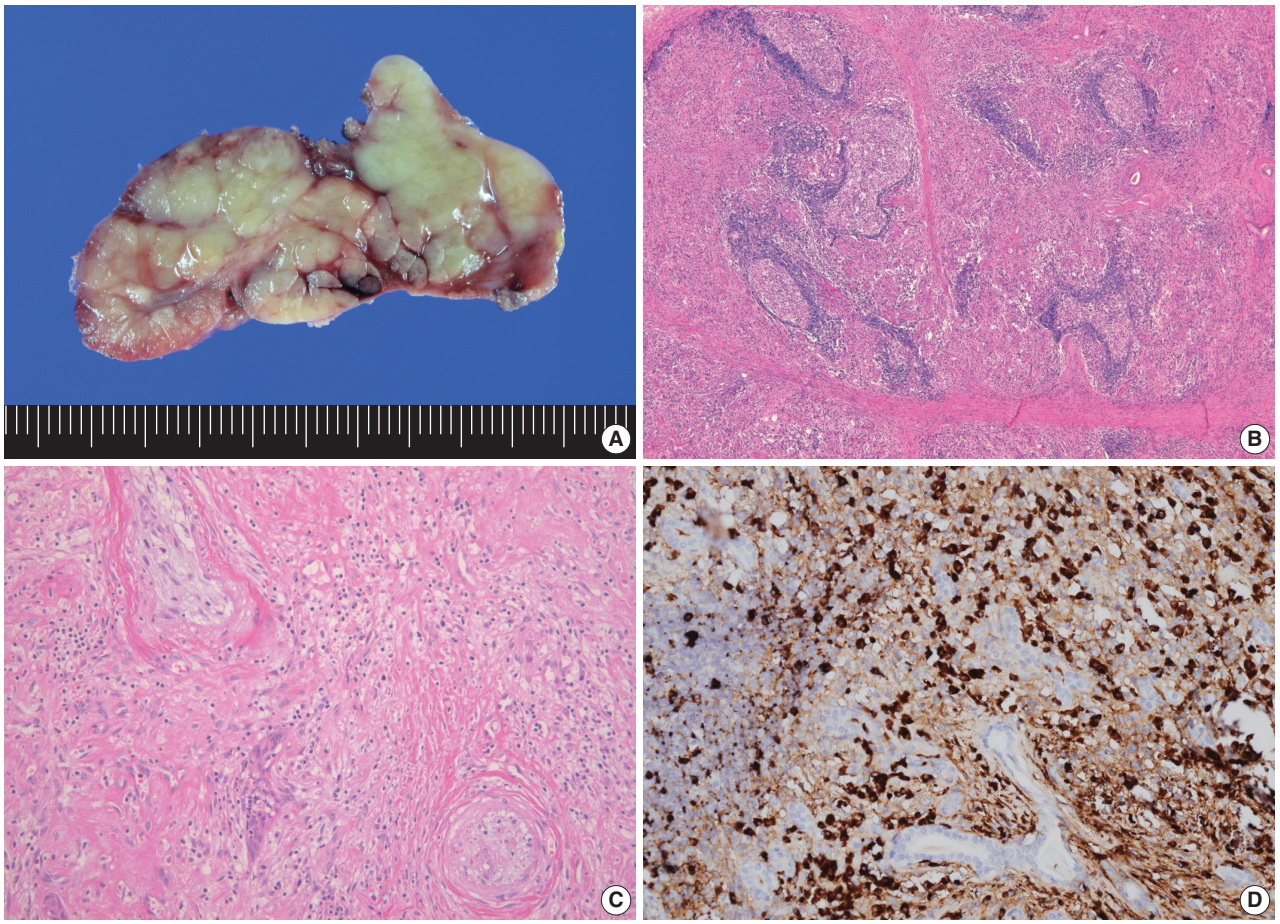

Fig. 1. The excised salivary gland preserves the lobular architecture with diffuse enlargement and multifocal fibrosclerotic areas (A). Histologic findings. The submandibular glands show lymphoplasmacytic infiltration with septal fibrosis (B) and obliterative phlebitis (C). Immunohistochemical results show numerous IgG4-positive cells (D) (IgG4 +cells, >60/high power fields).

lacrimal gland enlargement was reduced during physical examination at follow-up.

Case 2

A 62-year-old male presented with bilateral submandibular masses since last 4 months. He had a past medical history of stent insertion in the left ureter due to ureteric stricture in 2005, however, the accurate cause of the stricture was not known at that time. The head and neck CT revealed focal mass-like geographic low attenuation lesions with mild enhancement of submandibular glands. The abdominal CT showed a wedge-shaped

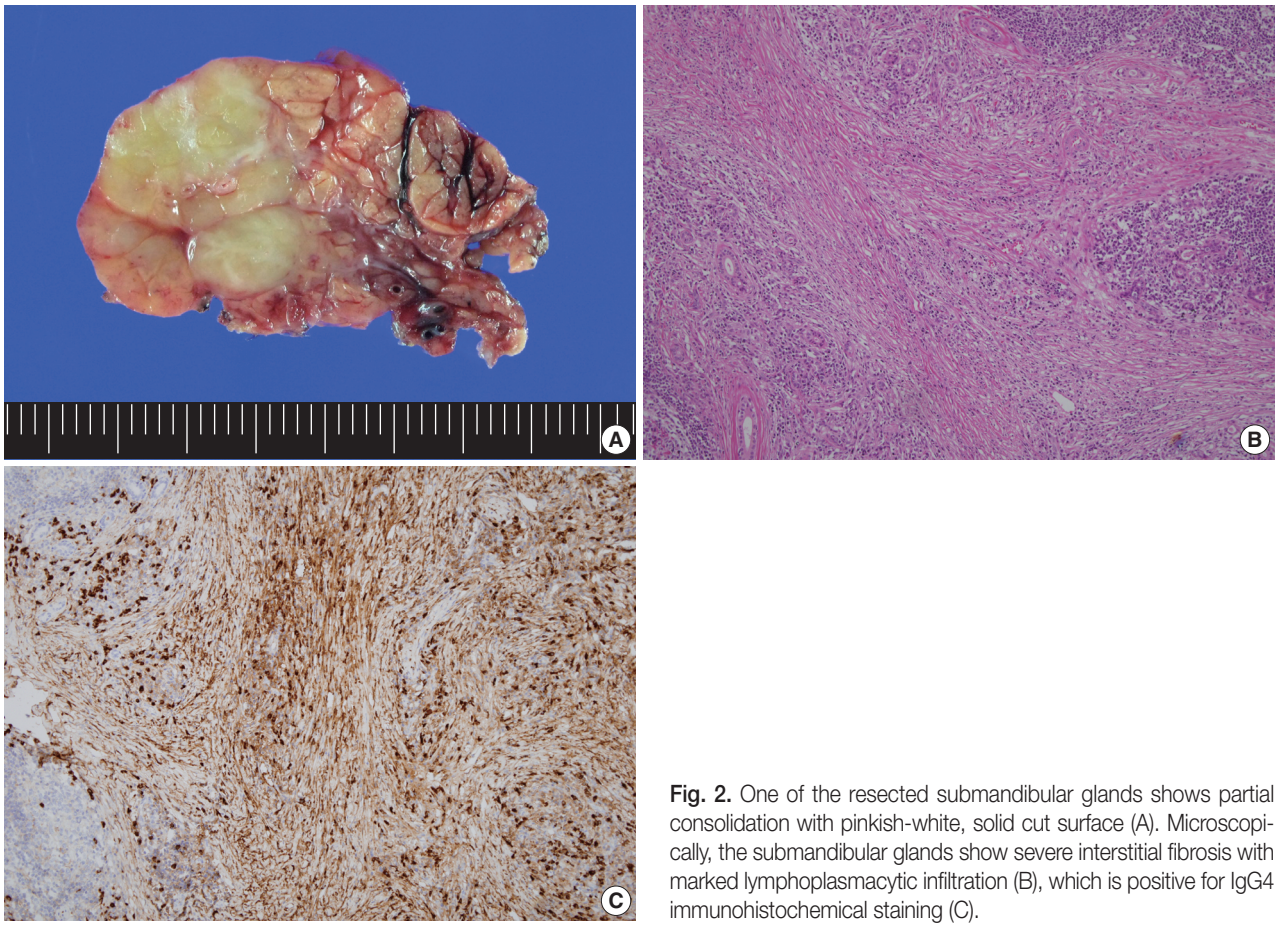

Fig. 2. One of the resected submandibular glands shows partial consolidation with pinkish-white, solid cut surface (A). Microscopically, the submandibular glands show severe interstitial fibrosis with marked lymphoplasmacytic infiltration (B), which is positive for IgG4 immunohistochemical staining (C).

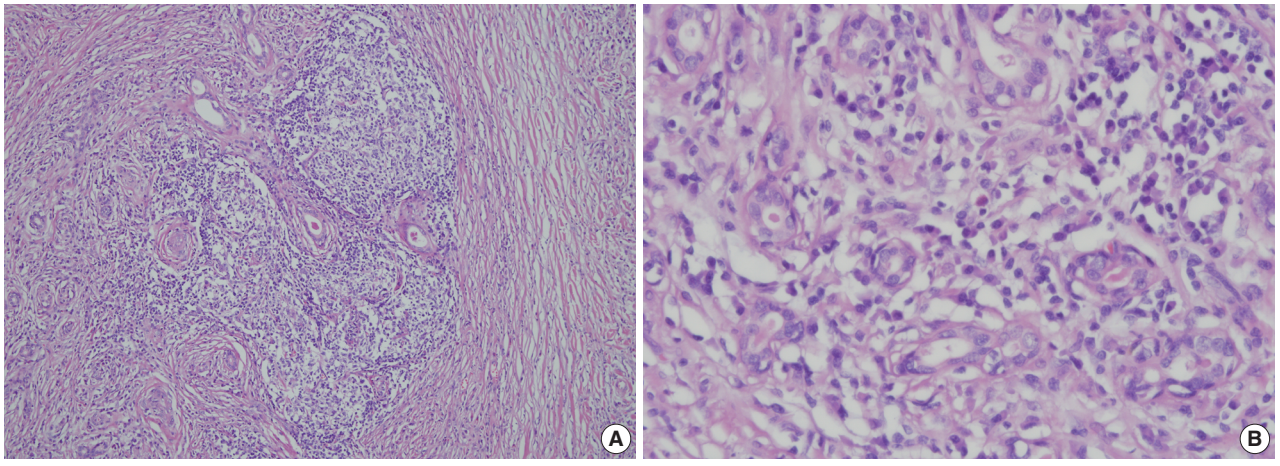

Fig. 3. (A, B) Microscopically, septal fibrosis and lymphoplasmacytic infiltration are identified.

low attenuation area in the upper pole of the left kidney with an inserted ureteral stent. Bilateral submandibular gland resection was performed. The resected submandibular glands were diffusely enlarged, measuring 3.5 cm in greatest dimension, with well-defined mass-like lesions measuring 3 cm in greatest dimension. The cut surface of the lesions was pinkish-white and solid with focal myxoid areas (Fig. 2A). Microscopically, the salivary glands showed severe interstitial fibrosis with marked lymphoplasmacytic infiltration around the salivary ducts and loss of the normal acinar structures (Fig. 2B). Immunohistochemical study revealed numerous IgG4-positive plasma cells in the background of CSS (Fig. 2C). The serum IgG level was elevated to 2,050 mg/dL before surgery, which was reduced to 1,690 mg/dL after the resection of submandibular glands (Table 1). The patient was treated with oral prednisolone (5 mg/day) and the renal and ureteral lesions are to be evaluated soon.

Case 3

A 55-year-old male presented with bilateral submandibular masses, and the right submandibular gland was surgically resected at an outside hospital. The patient was referred to our hospital for further evaluation. Microscopically, the resected specimen showed CSS with plasma cell components (Fig. 3). Immunohistochemical studies were not available at that time, but IgG4-related sialadenitis was suggested. During continued work-up, the patient was diagnosed with diabetes mellitus and oral medication was started. Three months later, he revisited our hospital for abdominal pain and poor oral intake. The physical examination, serologic tests and abdominal CT results revealed the possibility of autoimmune pancreatitis and extrapancreatic involvement, such as biliary dilatation due to distal common bile duct involvement, and multifocal involvement of the right kidney. The serum IgG and IgG2 levels were elevated to 1,950 mg/dL and 12.10 g/L respectively, but the level of IgG4 was not high at the time of evaluation (Table 1). The patient was treated with oral prednisolone (25 mg/day) medication and is awaiting a follow-up.

DISCUSSION

IgG4-related CSS (IgG4 CSS) is a recently established condition which is thought to be a part of systemic sclerosing disease. For unknown reasons, the disease characteristically affects the submandibular glands.[1] In 1888, Johann von Mikulicz-Radecki reported enlarged lacrimal and salivary glands with mononuclear cells infiltration, and in 1933, Sjögren described swelling of the major salivary gland which was termed as Sjögren's syndrome. Furthermore, in 1896, Küttner described chronic sclerosing sialadenitis. Recent studies reported that the pathogenesis of MD and KT is associated with the unusual cytotoxic T cell mediated process,[15] and these entities have been recently recognized as a part of the spectrum of IgG4-related sclerosing disease. IgG4 CSS is distinguished from Sjögren's syndrome in that it typically presents in the older age group with slight male predominance, persistent swelling, none to slight sicca syndrome, good response to steroid therapy, elevated serum IgG4/IgG ratio, negative antinuclear antibody and anti-SSA/SSB, and abundant IgG4-positive plasma cells in tissue.[4]

The pathogenesis of IgG4-related sclerosing disease is not completely understood. Increased serum levels of IgG and IgG4 and the presence of several autoantibodies in patients with pancreatitis raises a possibility of autoimmunity.[16] Also the presence of common targets in the pancreas and other exocrine organs, such as carbonic anhydrase (CA)-II, CA-IV, lactoferin, and pancreatic secretory trypsin inhibitor, distributed in the ductal cells of the pancreas and other organs has been suggested.[17] Recent studies have revealed immune complex deposition within tissues in IgG4-related sclerosing disease on electron microscopy. Increased levels of CD25-high expressing regulatory T cells and decreased levels of naive (CD45RA+) regulatory T cells have been reported to be associated with autoimmune pancreatitis.[16,17] Regulatory T cells usually inhibit immune responses by producing interleukin-10, however, they may also help to differentiate B lymphocytes into IgG4+ plasma cells. Biphasic mechanism of the disease, comprising of 'induction' and 'progression,' has been proposed.[16,17] Disease induction occurs due to an immune response to self-antigens and molecular mimicry, and this leads to a Th1 response and progresses to a Th2 response, differentiating B cells into plasma cells.[16,17]

Although the role of IgG4 is unknown at present, IgG4 participates as a common pathological component of sclerosing lesions in various organs, such as autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, tubulointerstitial nephritis, and interstitial pneumonia.[12] The lacrimal glands and pituitary gland are the least commonly involved organs in IgG4-related disease as recently described.[13,18]

In the present study, case 1 showed elevated serum IgG and IgG4 levels, while case 3 showed elevated IgG level and normal range of IgG4 level at the time of the test. However, the histologic features of the submandibular gland and the presence of

autoimmune pancreatitis in case 3 strongly support the diagnosis of IgG4 CSS. Also, if the follow-up data using oral prednisolone is favorable, it may help to confirm the diagnosis. Although serum IgG and IgG4 levels were not checked in case 2, the intraglandular presence of numerous IgG4 positive plasma cells supported the diagnosis of IgG4 CSS.

The cases in the present study are the first descriptions of IgG4 CSS cases in Korea. All cases showed lymphoplasmacytic infiltration in the resected submandibular gland specimens and elevated serum IgG and/or IgG4 levels. The three cases differed in the type and extent of systemic involvement. Case 1 had accompanying dacryoadenitis and hypophysitis, case 2 had previous ureteral stricture, and case 3 had accompanying pancreatic and bile duct involvement. The reported IgG4 CSS cases were accompanied with retrobulbar neuritis,[19] retroperitoneal fibrosis,[3] cholangitis,[2] pancreatitis,[5] and prostatitis.[5] It appears that systemic involvement in IgG4 CSS is variable in combination case by case, and may vary with time.

In summary, it is not yet determined whether IgG4 CSS is a specified disease entity and the role of plasma cells is specific, however, salivary gland involvement in IgG4-related fibrosclerosis should be recognized in systemic pathology to avoid unnecessary surgery and to seek systemic evaluation.

REFERENCES

1. Isacsson G, Ahlner B, Lundquist PG. Chronic sialadenitis of the submandibular gland: a retrospective study of 108 case. Arch Otorhinolaryngol 1981; 232: 91-100.
2. Tsuneyama K, Saito K, Ruebner BH, Konishi I, Nakanuma Y, Gershwin ME. Immunological similarities between primary sclerosing cholangitis and chronic sclerosing sialadenitis: report of the overlapping of these two autoimmune diseases. Dig Dis Sci 2000; 45: 366-72.
3. Sekine S, Nagata M, Watanabe T. Chronic sclerosing sialadenitis of the submandibular gland associated with idiopathic retroperitoneal fibrosis. Pathol Int 1999; 49: 663-7.
4. Yamamoto M, Harada S, Ohara M, *et al.* Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. Rheumatology (Oxford) 2005; 44: 227-34.
5. Kitagawa S, Zen Y, Harada K, *et al.* Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). Am J Surg Pathol 2005; 29: 783-91.
6. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. J Gastroenterol 2006; 41: 613-25.
7. Zen Y, Harada K, Sasaki M, *et al.* IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol 2004; 28: 1193-203.
8. Zen Y, Kitagawa S, Minato H, *et al.* IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung. Hum Pathol 2005; 36: 710-7.
9. Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. Am J Gastroenterol 2003; 98: 2811-2.
10. Dooreck BS, Katz P, Barkin JS. Autoimmune pancreatitis in the spectrum of autoimmune exocrinopathy associated with sialoadenitis and anosmia. Pancreas 2004; 28: 105-7.
11. Hamano H, Kawa S, Ochi Y, *et al.* Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet 2002; 359: 1403-4.
12. Kamisawa T. IgG4-related sclerosing disease. Intern Med 2006; 45: 125-6.
13. Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4-related sclerosing disease? Am J Surg Pathol 2007; 31: 643-5.
14. van der Vliet HJ, Perenboom RM. Multiple pseudotumors in IgG4-associated multifocal systemic fibrosis. Ann Intern Med 2004; 141: 896-7.
15. Tiemann M, Teymoortash A, Schrader C, *et al.* Chronic sclerosing sialadenitis of the submandibular gland is mainly due to a T lymphocyte immune reaction. Mod Pathol 2002; 15: 845-52.
16. Bateman AC, Deheragoda MG. IgG4-related systemic sclerosing disease: an emerging and under-diagnosed condition. Histopathology 2009; 55: 373-83.
17. Okazaki K, Uchida K, Fukui T. Recent advances in autoimmune pancreatitis: concept, diagnosis, and pathogenesis. J Gastroenterol 2008; 43: 409-18.
18. Chan SK, Cheuk W, Chan KT, Chan JK. IgG4-related sclerosing pachymeningitis: a previously unrecognized form of central nervous system involvement in IgG4-related sclerosing disease. Am J Surg Pathol 2009; 33: 1249-52.
19. Abe T, Sato T, Tomaru Y, *et al.* Immunoglobulin G4-related sclerosing sialadenitis: report of two cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 108: 544-50.