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Giant Necrotizing Ulcers in the Oral Cavity and Gastro-Intestinal Tract Associated with IgA(K)-IgG Cryoglobulinemia

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Two males exhibited giant necrotizing tissues involving lateral one-half of the hard palate in the oral cavity. There were multiple, giant and nectoric ulcers concomitantly in the esophago-gastro-intestinal tracts, leading to perforations at the ileum and subsequent peritionitis. Soft palate in the oral cavity of nasal cavities was not involved. Mixed cryoglobulinemia of IgA(K)-IgG type was seen in both cases without proteinuria. Histological findings revealed of necrotizing ulcer with proliferation of plasma cells, lymphocytes and macrophages. Partial abscess formations were also present. There was no evidence of angitis, granuloma, reticulosis or gastrinsecreting tumor. These clinical features appear to be unique and so far not documented in the literature.

Key words
Necrotizing ulcers,
Oral cavity,
Gastro-Intestinal tracts,
Cryoglobulinemia.

INTRODUCTION

Necrotizing ulcers in the oral cavity is a rare and striking clinical feature. We have experienced two male patients with unusual clinical features of a marked necrotizing ulcers throughout the digestive tract from the oral cavity to the small intestine complicated by perforations and peritonitis. Differential diagnosis included, Wegener's granuloma (1), allergic angitis and granulomatosis (2), periarteritis nodosa (3), necrotizing rhinitis (4), malignant reticulosis (5), syphilis, SLE, Behçet's disease, or Zollinger-Ellison syndrome.

CASE PRESENTATION

Major clinical characteristics in both cases are summarized in Table 1.

Case 1, M.O., 47 year-old male, shoemaker, experienced an unusual sensation in the right side of the hard palate in the oral cavity, where a necrotizing mass developed around the right 7th and 8th upper teeth was noted on December 1975. The necrotizing tissues gradually increased in size and resisted corticosteriod therapy.

IgA(K)-IgG cryoprecipitations were detected in the serum as shown in Figure 1A. Urinary protein was negative. CRP + 3 and ESR 50 mm/hr was recorded. Laboratoy data were otherwise

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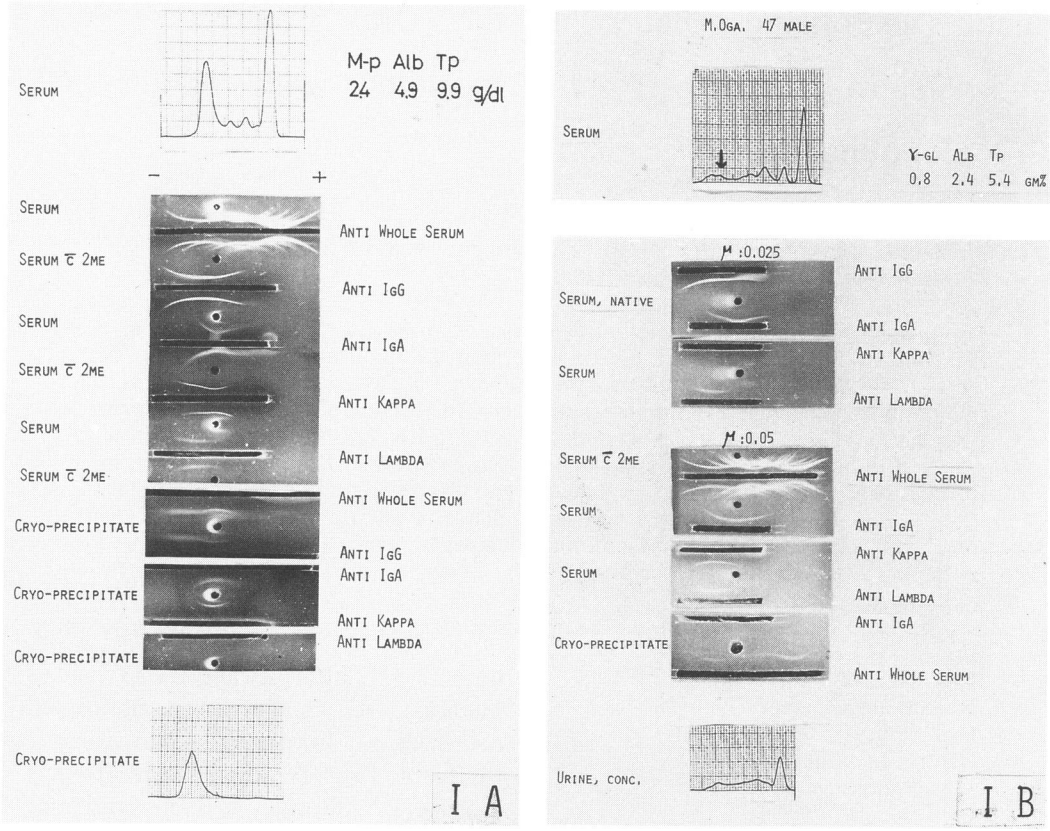

Figure 1. Cellulose Acetate electrophoresis and agarose immunoelectrophoresis on the native and extracted cryoglobulin, consisting of IgA(K), IgG and residual albumin. On routine electrophoresis, there are a prominent spike of gamma mobility in Case 1 and a small spike (Arrow) in Case 2. There is some effect of 2-ME for dissociation of cryoglobulin and euglobulin property in Case 1 (1A) and Case 2 (1B).

unremarkable. Immunological data including ANF, rheumatoid factor, complement or LE cells were negative. He had recurrent epiqastric pains and was found to have a giant gastric ulcer by X-ray as shown in 3A. A gastrin level was 295 pg/ml in the fasting serum. Massive bleedings were experienced from the progressively excavated oral cavity in February 1976. A biposy of a left cervical lymph mode showed lymphadenitis with the proliferations of plasma cells. An acute abdominal pain led to laparotomy which disclosed marked exsudates and a perforation of the ileum about 60 cm orally from the ileocaecal region. A partial resection of the ileum was performed, but he died of acute peritonitis on April 1. 1976.

Autopsy findings included a necrotic lesion in the right oral cavity(Fig 2A), small ulcers in the esophagus, a giant ulcer 13 × 7 cm in size along with smaller ulcers of various size in the

Table 1: Major clinical data of 2 cases.

	Case 1	Case 2
Age and sex	47 male	69 male
Necrotizing ulcers		
hard palate, unilateral	+	+
soft palate	-	-
naso-pharynx	-	-
stomach	+	+
duodenum	+	+
ileum	+	+
Perforations of the ileum and peritonitis	+	+
Histology of the ulcers		
Plasma cell proliferations	+	+
angitis	-	-
granuloma	-	-
Cryoglobulinemia	IgA(κ)-IgG	IgA(κ)-IgG

stomach, four ulcers of about 0.5 to 1 cm in diameter in the duodenum and a perforated ulcer with abscess in the ileum about 60 cm orally form the end of the caecum. Histologically, proliferation of lymphocytes, plasma cells and macrophages were noted in the necrotizing tissues of the oral cavity, whereas lymphocytes and plasma cells were predominant in the deep muscle layers of ulcerative tissues of the esophagus, stomach, duodenum and ileum. No vascular changes in the involved tissues were noted. No findings suggesting tuberculosis, syphilitic or other glanulomatous changes were obtained.

Case 2, K.B., 69 year-old male, smith, started to notice shortness of breath, recurrent epistaxis and auditory difficulty in the right ear in 1966. On examination, he was anemic with fingers and toes turning purple-whitish on exposure to cold. Laboratory data included decreased hemoglobin 6.3 g/dl, the proliferations of plasma cells (25.6%) in the bone marrow and the presence of IgA(K)-monoclonal protein in the serum. No diagnosis of plasma cell myeloma

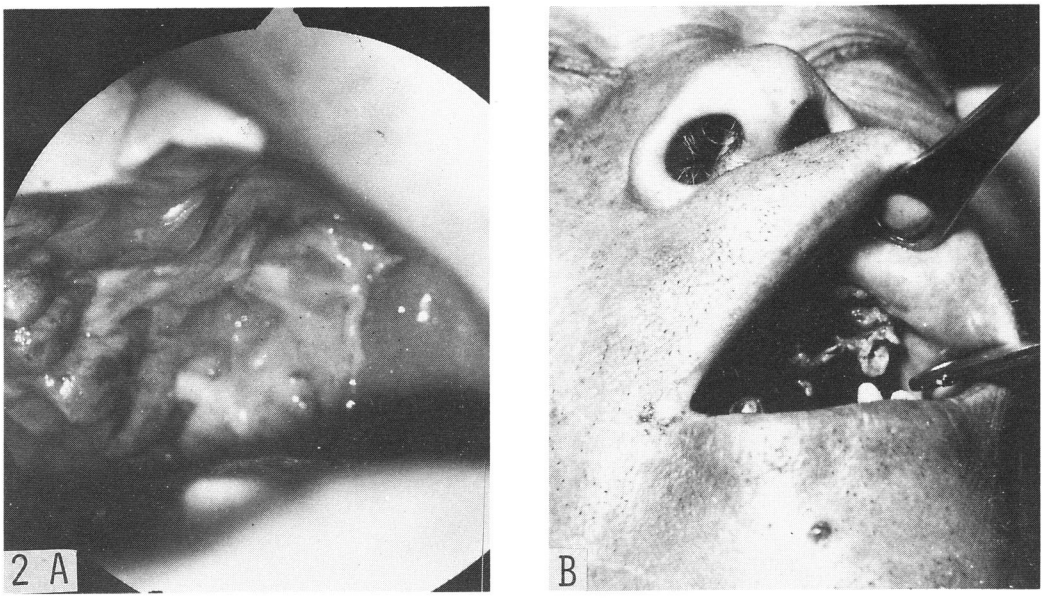

Figure 2. Oral ulcers in Case 1 (2A) and Case 2 (B).

was made because of the absence of bone changes. IgA(K)-IgG cryoprecipitations were detected in the serum as in Figure 1B. Urinary protein was negative. Other laboratory data were unremarkable. Fluoroscopy of the upper gastro-intenstinal tract revealed a giant ulcer in the cardia (3 × 3 cm by X-ray) and ulcers in the cap and descending portions of the duodenum as shown in 3B. A gastrin levels was 341 pg/ml in the fasting serum. Figure 1B showed electrophoretic patterns on cellulose acetate revealing the spike of γ-mobility in the serum of May 1, 1967, which tended to normalize in contour along the clinical course without any anti-cancer or anti-inflammatory drugs except for injection of hydrocortisone of a total dose 80 mg.

Subsequent course was characterized by massive necrosis in the left side of the hard palate in the oral cavity (Fig 2B). Massive blood repeatedly occurred from the necrotizing tissues. Histological examination of the sharply demarcated necrotic tissues showed ulcerative, but not granulomatous changes with plasma cells, lymphoytes and macrophages. Ulcer were also seen in the anus.

A sudden onset of left lower abdominal pain with tenderness led to a surgical operation. A perforation was detected about one meter orally from the end of the caecum, along with grey, multiple and deeply excavated ulcers. A partial resection of the ileum was performed. Histological examination of the ulcer revealed necrotizing defect of the mucous membrane, covering an area of phlegmonous infiltration by neutrophils. In the deep muscular layers, marked infiltration by plasma cells, new formations of capilaries, and small numbers of lymphocytes and

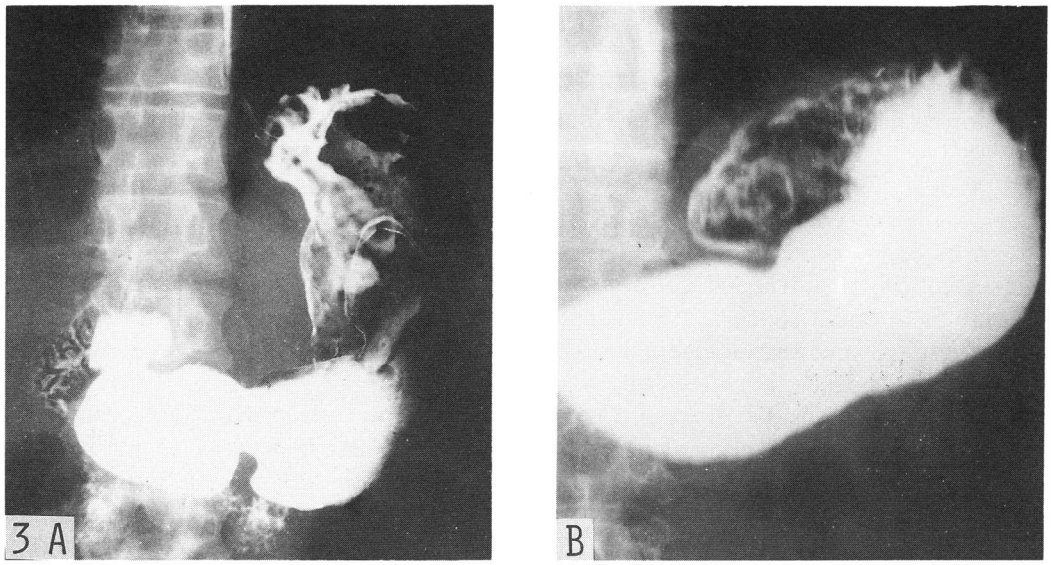

Figure 3. Giant ulcers in the stomach by fluoroscopic examinations on X-ray in Case 1 (3A) and Case 2 (B).

eosinophils were seen. There were no histological evidence of granulomatous changes of findings suggestive of fungal infections. His general condition deteriorated and died of peritonitis on September 2, 1967. Permission of autopsy was not obtained.

DISCUSSION

The 2 patients described above had giant necrotizing ulcers in the oral cavity and multiple ulcers in the gastrointestinal tracts followed by acute peritonitis due to perforations or anastomosis failure after operation in the GI-tracts. Histological examinations confirmed the presence of multiple ulcers in the gastro-intestinal tracts with no evidence of angitis or vasculitis.

For the differential diagnosis of necrotizing tissues, the following clinical entities are to be listed. Wegener's granulomatosis (1,2) is characterized by necrotizing granulomas in the respiratory tract, necrotizing vasculitis of the small arteries and focal glomerulonephritis. Allergic angitis and granulomatosis (3) is characterized by a well-defiend clinical syndrome of asthma, fever, and hypereosinophilia with granulomatous lesions of respiratory tracts and angitis of small size. The present cases showed clinical and histological findings distinctly different from these disease categories.

Necrotizing rhinitis (6), lethal midline granuloma, midline malignant reticulosis, granuloma gangrenescens and malignant granuloma (2,5) belong to the same group of clinical entity, being characterized by necrosis in the nasal cavity and soft palate (but not hard palate), associated with proliferations of histiocytes, lymphocytes and some plas-

ma cells. Tendency to necrosis was not seen in reticulosis (7) or reticulum cell sarcoma, where monotonous proliferations of reticulum cells are characteristic.

Syphilitic or tuberculous processes, granulomatous colitis, regional colitis or granulomatous colitis or Schistosomiasis colitis, the dreaded cellulitis of the submandibular space could not cover the clinical and histological pictures of the present cases. Periarteritis nodosa (4), SLE or Behçet's disease do not also correspond to the clinical varieties or laboratory data in the present cases. Cases here are also not classified as multiple myeloma (5), since cytological features of plasma cells appeared as mature and there was the abscence of bone lesion.

In Zollinger-Ellison syndrome, characterized by multiple gastrointestinal ulcers and high serum gastrin levels, an association of necrotizing ulcer in the oral cavity has not been described in the literature.

The present cases do not belong to any of these disorders and apparently represent an unusual set of clinical manifestations, hardly described in the literature so far.

Necrotizing vasculitis is a term to describe vessel wall necrosis due to neutrophil infiltration. Current evidence strongly suggests that these cells are responding to elaboration of chemotactic factors of the complement cascade released at the site of deposition of immune complexes in the vessel walls. The present cases may be relevant to this disorder, although the pricise actions of complement were yet unknown.

It is interesting that IgA-associated cryoglobulinemia were seen in the present cases, in connection with the defence mechanism of IgA at the external surface of G-I tracts (10) and the relative rarity of IgA cryoglobulin in the literature (11). IgA(K)-M-proteins may be a result of presumably transient proliferations of plasma cells in the G-I tracts and in the marrow after the long-standing stimuli of unknown etiology in the clinical course. Mixed cryoglobulin of kappa type monoclonal IgA and polyclonal IgG might be related to clinical manifestations in the present cases. The role of IgA-IgG cryoglobulin responsible for the necrotizing ulcer in alimentary tract is worthy of pursuit.

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