

Repeated Massive Tongue Swelling Due to the Combined Use of Estramustine Phosphate and Angiotensin-Converting Enzyme Inhibitor

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Abstract. A 70-year-old man presenting with a chief complaint of tongue swelling had been diagnosed with prostate cancer 1 year earlier. He had been on an oral angiotensin-converting enzyme inhibitor (ACE) inhibitor for hypertension for 20 years. Two months before the first of 4 episodes of tongue swelling within a period of 40 days, he had been prescribed oral estramustine phosphate (EMP) for the prostate cancer. He was admitted to our hospital for the evaluation after massive swelling of the tongue and epiglottis which necessitated tracheotomy. Food allergies, allergic reactions to environmental factors, and hereditary angioneurotic edema were excluded. Massive swelling of the tongue and epiglottis disappeared completely after EMP was discontinued. We concluded that angioedema was induced by EMP used concurrently with the ACE inhibitor.

Key Words: Estramustine phosphate. Angiotensin-converting enzyme inhibitor. Angioedema. Tracheotomy. Prostate cancer.

Resumen. A un paciente de 70 años de edad con edema lingual como motivo principal de consulta, le había sido diagnosticado un cáncer de próstata un año antes. Había estado tomando un inhibidor oral de la enzima convertidora de la angiotensina (IECA) para el tratamiento de la hipertensión durante 20 años. Dos meses antes del primero de los cuatro episodios de edema de la lengua, se le había prescrito fosfato de estramustina oral para el cáncer de próstata. Fue ingresado en nuestro hospital para su observación tras el edema lingual masivo y la epiglotis que requirió practicarle una traqueotomía. Se descartaron alergias alimentarias, reacciones alérgicas a factores medioambientales y edema angioneurótico hereditario. El edema masivo de lengua y epiglotis desaparecieron completamente tras cesar la administración de fosfato de estramustina. Concluimos que el angioedema fue causado por el uso simultáneo del fosfato de estramustina y el IECA.

Palabras clave: Fosfato de estramustina. Inhibidor de la enzima convertidora de la angiotensina. Angioedema. Traqueotomía. Cáncer de próstata.

Introduction

Estramustine phosphate (EMP), a drug for the treatment of prostate cancer, is a compound resulting from the chemical combination of the estrogen preparation estradiol and the alkylating agent nitrogen mustard. EMP accumulates in cancer tissue through the activity of the estramustine-binding protein present in prostate cancer tissue. It exhibits cytotoxic activity by inhibiting the polymerization of microtubules [1]. EMP has been said to rarely produce angioedema as a side effect [2]. It has been suggested, though not documented, that the combined use of an angiotensin-converting enzyme (ACE) inhibitor and EMP does facilitate the development of EMP-induced angioedema. We report a case in which the combined use of EMP and an ACE inhibitor induced severe angioedema requiring tracheotomy.

Case Description

The patient was a 70-year-old man with a chief complaint of massive tongue swelling. He had a 30-year history of hypertension, hyperlipidemia, and hyperuricemia, and was diagnosed with prostate cancer in April 2004. He had no history of allergies to foods or drugs. He had been taking an ACE inhibitor for hypertension for 20 years. EMP was newly prescribed for his prostate cancer in December 2004.

On February 5, 2005, swelling of the tongue erupted at around 1 PM, starting on the right side (Figures 1 and 2). Despite the intravenous administration of 500 mg of hydrocortisone, the swelling extended to the base of the tongue and the epiglottis, making tracheotomy necessary. The swelling subsided spontaneously in 24 hours. On February 18, 2005, swelling of the right side of the tongue started without any precipitating events at about 5 PM; it extended to the base of the tongue but gradually subsided after the administration of 300 mg of hydrocortisone. On March 7, 2005, local edema appeared in the right cheek at about 11 AM, but gradually subsided after the administration of 300 mg of hydrocortisone. On March 19, 2005, swelling of the right side of the tongue appeared and extended to the floor of the mouth. The administration of 600 mg of hydrocortisone did not improve the swelling, but additional administration of 300 mg of the hormone resulted in the subsidence of the swelling on the following day. To determine the causes of the 4 episodes of swelling of the tongue and epiglottis within such a short period of time, we admitted him to our department.

On admission, he was 171 cm tall and weighed 61 kg. He was conscious and his temperature was 35.3°C; blood pressure, 130/80 mm Hg; and pulse rate, 72 beats/min. He had no signs of anemia or jaundice in the palpebral or bulbar conjunctivae and no superficial lymph nodes were palpable. Heart and breath sounds were normal. The abdomen was flat, soft, and free of tenderness. Neither the liver nor the spleen was palpable.



Figure 1. Massive tongue swelling observed at its first episode.



Figure 2. Marked swelling in the mandible and anterior cervical regions. The cervical swelling reflected lingual and pharyngeal swelling.

Examination of the extremities and skin revealed no abnormalities. Neurological findings were all normal. On admission, laboratory data were as follows: white blood cells, 10 600/ μ L; slightly elevated C-reactive protein, 0.26 mg/dL; hemoglobin, 9.9 g/dL with a hematocrit of 29.5%; and markedly elevated prostate specific antigen, 234.9 ng/mL. There were no abnormalities in eosinophils, immunoglobulin E, or C3, C4, or C1 inactivators. Urinalysis showed no apparent abnormalities except for mild proteinuria. Drug lymphocyte stimulation tests for EMP and the ACE inhibitor cilazapril, which the patient was taking at the time of admission, were negative.

After admission, EMP alone, which the patient had started to take recently, was discontinued, but he continued to take the ACE inhibitor because he had been taking it for 20 years without developing angioedema. As a result, he has since been free of swelling episodes while being followed on an outpatient basis.

Discussion

This patient had 4 episodes of massive swelling in the tongue, face, and pharynx within a period of 40 days. Although, the episodes were initially attributed to food allergy, that cause was excluded in the absence of a definite relationship between food intake and the timing of swelling episodes. In addition, the location of swelling varied, excluding allergic reactions to environmental factors. Moreover, blood test results excluded hereditary angioneurotic edema.

A detailed analysis of the course of the patient's condition suggested that the swelling could be the side effect of the EMP taken for prostate cancer since December 2004. Therefore, the oral administration of EMP was discontinued. As a result, the patient has since been free of similar swelling episodes, leading to a diagnosis of EMP-induced angioedema.

It has been suggested that the combined use of EMP and an ACE inhibitor increases the incidence of angioedema. An ACE inhibitor alone causes angioedema in only 0.1% to 0.5% of cases [3]. ACE inhibitors have been reported to inhibit not only the conversion of angiotensin I to angiotensin II but also kininase II activity, which is important for bradykinin inactivation. Therefore, we speculate that ACE inhibitors might increase the local concentration of vasoactive kinin in the subcutaneous tissue and that EMP aggravates it, leading to the development of angioedema [4, 5] under some circumstances. Occurrence of angioedema by possibly reducing the activity and amount of C1-esterase inhibitor is reported in patients taking estrogens [6, 7]. Therefore, another possible mechanism is that EMP might have decreased the level of C1-inhibitor protein in this patient, who had already been sensitized to angioedema under long-term use of ACE inhibitors. However, serum levels of C1-esterase inhibitor protein and activity were not evaluated longitudinally in this case, so the relevance of this possible mechanism is speculative.

Severe angioedema causing massive tongue swelling after taking EMP, as a side effect, has rarely been reported

worldwide. Moreover, until now, no case of severe swelling of the tongue and epiglottis requiring tracheotomy had been reported.

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