

($n = 8$) of sputum preparations stained by Giemsa, macrophages were 41% (range = 7.8% to 82.0%) and eosinophils were 31% (range = 16.4% to 87.7%) of the total cell count. In cytopsins stained by the APAAP method ($n = 8$), the GM-CSF-positive cells were 36% (range = 15.6% to 42.7%) of the total cell count. Macrophages comprised 54% (range = 18.1% to 94.1%) and eosinophils 45% (range = 6.4% to 81.8%) of GM-CSF-positive cells (Fig. 1, A and C). EG-2-positive eosinophils cells ($n = 8$) were 10% (range = 0.6% to 72.5%) of the total cell count (Fig. 1, D). No cells were stained by IgG₁ ($n = 8$) (Fig. 1, B).

In conclusion, GM-CSF-containing cells and activated (EG-2-positive) eosinophils were demonstrated in sputum. The presence of GM-CSF in sputum cells could represent GM-CSF synthesis by the cells identified or production of GM-CSF by other cells with subsequent attachment to GM-CSF receptors. The effective processing of sputum by methods such as those described here can be expected to permit additional studies such as in situ hybridization with probes to detect

cytokine messenger RNA. This approach adds another dimension to the use of sputum to examine inflammatory cell responses in lung diseases.

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Late-onset angioedema after interruption of angiotensin converting enzyme inhibitor therapy

Philip Dennis Dyer, MD Aurora, Colo.

Angioedema is an infrequent complication resulting from the use of angiotensin converting enzyme (ACE) inhibitors. The overall incidence has been reported to be 0.1% to 0.2%, and the time of onset is usually during the first week of therapy.¹ Sporadic cases documenting episodes of angioedema that developed weeks to months after initiation of ACE inhibitor therapy have appeared in the literature. The following case report is an example of late-onset angioedema, which may have been precipitated by a temporary cessation of therapy.

CASE REPORT

A 55-year-old woman was being followed up for osteoarthritis and hypertension and was receiving enalapril 5 mg two times a day, which provided good control of her hypertension. The enalapril was prescribed 7 months earlier without any noted complications. She discontinued therapy for 72 hours pending a refill of her enalapril. On the third day of resuming the enalapril, she noticed tongue fullness about 1 hour after taking her morning dose. Approximately 1 hour after her next dose, she experienced precipitous tongue swelling that resulted in stridor and dyspnea. She immediately went to the local emergency room and was diagnosed as having acute upper airway obstruction caused by angioedema of the tongue. Her tongue was actually protruding from her mouth because of the angioedema. She was emergently intubated and treated with epinephrine, Solu-Medrol, diphenhydramine, and cimetidine. After intubation was performed, respiration was easily maintained with a T-tube and 30% oxygen. Further physical examination revealed that the lungs

From the Allergy/Immunology Services, Fitzsimons Army Medical Center, Aurora.

Reprint requests: P. Dennis Dyer, MD, Allergy/Immunology Service, Fitzsimons Army Medical Center, Aurora, CO 80045.

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TABLE I. Time of onset of delayed angioedema

Study	No. of cases	Time of onset
Slater et al. ¹	26	3 wk-11 mo
Jain et al. ⁴	3	3-10 mo
Hedner et al. ⁵	11	3 wk-1 yr

were free of wheezing and the skin was without urticaria. An examination by an otolaryngologist detected swelling of the tongue and posterior oropharynx without involvement of the laryngeal pharynx. Her angioedema receded over the ensuing hours, and she was extubated 16 hours later without further complications. She was discharged after a 24-hour hospitalization without sequelae, and nifedipine was substituted for her enalapril. During subsequent evaluation in the allergy clinic, the patient denied any personal or family history of angioedema. She had no history of drug or food allergies, and her food skin test panel results were negative. Her complement studies revealed a total hemolytic complement CH50 of 282 U/ml (range, 101 to 300 U/ml), C4 of 31 mg/dl (range, 15 to 45 mg/dl), and C3 of 170 mg/dl (range, 85 to 193 mg/dl). Results of physical examination were also within normal limits. A recent conversation with the patient revealed that she had experienced no further angioedema in the 6 months after the initial event.

DISCUSSION

This case is an example of late-onset angioedema that developed during the seventh month of enalapril therapy, instead of the usual first week of therapy. Most of the literature suggests that time of onset is usually within the first week of ACE inhibitor therapy.^{2, 3} Angioedema in this case developed during the seventh month but actually occurred on the third day of resumption of therapy after a temporary cessation. Several other authors have summarized individual cases or reviewed pooled data on angioedema that occurred later in the course of therapy.^{1, 4, 5} Table I shows the time of onset of angioedema in some of these cases. Slater et al.¹ noted 26 cases with onset between the third week and the eleventh month of therapy in a pool of 36,050 patients. There was no temporal trend noted for occurrence outside the first week. The above-men-

tioned cases are attributed to the ACE inhibitor, because the patients experienced their first episode of angioedema during therapy. In several of the above-mentioned individual case reports, normal complement studies are reported to exclude the hereditary and acquired form of angioedema; this in itself does not exclude idiopathic angioedema. Though idiopathic angioedema may be the actual diagnosis in some of the cases, late-onset angioedema caused by ACE inhibitors represents a serious clinical entity. This case indicates that an interruption in ACE inhibitor therapy may represent a possible risk factor for late-onset angioedema.

When ACE inhibitors are prescribed, patients should be cautioned about angioedema and informed about its precipitous and threatening consequences. In addition, patients may need to be warned about temporarily discontinuing therapy. Preexisting angioedema, regardless of the cause (including chronic urticaria and angioedema), should be a contraindication for ACE inhibitor therapy. Patients with a history of late-onset angioedema while receiving ACE inhibitors should be questioned about their recent medication history and asked whether any break in ACE inhibitor therapy occurred. This information could eventually be helpful in delineating the causes of late-onset angioedema secondary to ACE inhibitor therapy and could facilitate a strategy to prevent this clinical entity. Most importantly, late-onset angioedema should alert the clinician to discontinue the ACE inhibitor to prevent further morbidity.

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