Clinical Challenge | PATHOLOGY

Persistent Epiglottic Swelling With Ulceration

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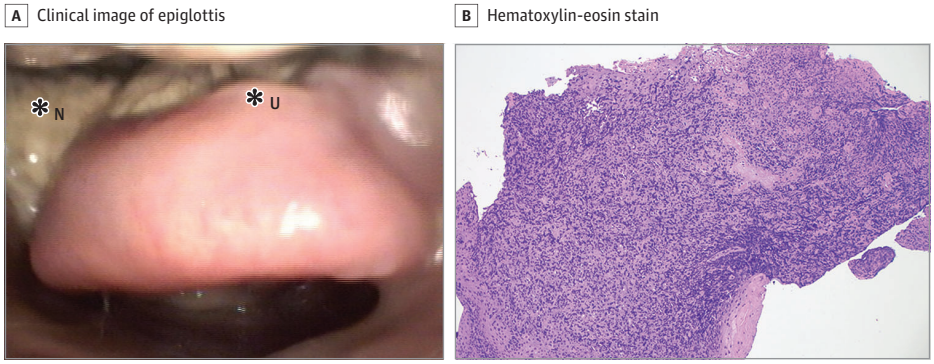

Figure 1. A, Flexible laryngoscopy showed a markedly enlarged, hemispheric epiglottis with abundant yellow necrotic material, indicated by N, and focal ulceration, indicated by U. B, Histopathology showed diffuse infiltration by atypical lymphoid cells with effacement of normal mucosal architecture (original magnification, ×10).

A 62-year-old man presented to the otolaryngology department with progressive odynophagia and a foreign-body sensation in the throat for 1 month without dyspnea. Flexible laryngoscopy at an outside hospital revealed marked epiglottic edema and hyperemia, and he was treated for acute epiglottitis with intravenous ceftriaxone, metronidazole, and corticosteroids for 1 week. Throat pain improved, but supraglottic swelling persisted. His symptoms subsequently worsened, and repeat treatment with broad-spectrum antibiotics and corticosteroids produced no substantial improvement. Two days before presentation, he developed fever with a maximum temperature of 39.2 °C/102.6 °F.

Flexible laryngoscopy showed a markedly enlarged epiglottis with abundant yellow necrotic material and focal ulceration (**Figure 1**A). Contrast-enhanced neck magnetic resonance imaging demonstrated diffuse thickening of the epiglottis and adjacent supraglottic mucosa with heterogeneous enhancement, without evidence of a deep neck space abscess. Chest computed tomography showed multiple bilateral pulmonary nodules. Plasma Epstein-Barr virus (EBV) DNA was detected. The initial biopsy results were nondiagnostic. Repeat direct laryngoscopic biopsy showed effacement of the normal mucosal architecture, and hematoxylin and eosin staining demonstrated diffuse sheets of atypical lymphoid cells (Figure 1B). Immunohistochemistry was positive for CD2, cytoplasmic CD3ε, CD7, granzyme B, and weak CD56 and negative for terminal deoxynucleotidyl transferase; CD20 highlighted only rare background lymphocytes. In situ hybridization detected EBV-encoded RNA (EBER).

WHAT IS YOUR DIAGNOSIS?

- **A.** Bacterial epiglottitis with occult abscess
- **B.** Laryngeal tuberculosis
- **C.** Supraglottic squamous cell carcinoma
- **D.** Extranodal natural killer/T-cell lymphoma, nasal type

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Diagnosis

D. Extranodal natural killer/T-cell lymphoma, nasal type.

Discussion

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL), is an aggressive EBV-associated lymphoma that classically involves the nasal cavity and other sites of the upper aerodigestive tract.[1,2] Although traditionally termed *nasal type*, ENKTL can also arise at extranodal sites outside the nasal cavity, and primary laryngeal involvement is uncommon. In such cases, patients may present with odynophagia, dysphagia, hoarseness, cough, or a foreign-body sensation.[3] Because endoscopic findings may be limited to nonspecific edema, exudate, or ulceration, diagnostic delay is common, and patients often receive empiric antibiotics and corticosteroids before biopsy.[3]

Definitive diagnosis of ENKTL requires adequate tissue sampling; histopathology typically shows an angiocentric/angiodestructive lymphoid infiltrate with prominent apoptosis and coagulative necrosis, whereas superficial biopsies may reveal only necrosis and secondary inflammation, necessitating repeat sampling when clinical suspicion is high.[1,4] The immunophenotype of ENKTL typically includes CD2 positivity, cytoplasmic CD3ε positivity, surface CD3 negativity, CD56 positivity, and expression of cytotoxic molecules such as TIA-1, perforin, or granzyme B (**Figure 2**). EBER positivity on in situ hybridization is a key diagnostic feature, but it is not sufficient by itself to establish the diagnosis of ENKTL, because other EBV-associated lymphoproliferative disorders may show similar findings.[1,4] Detection of plasma EBV DNA should raise clinical suspicion.[5] Imaging alone cannot reliably distinguish ENKTL from in-

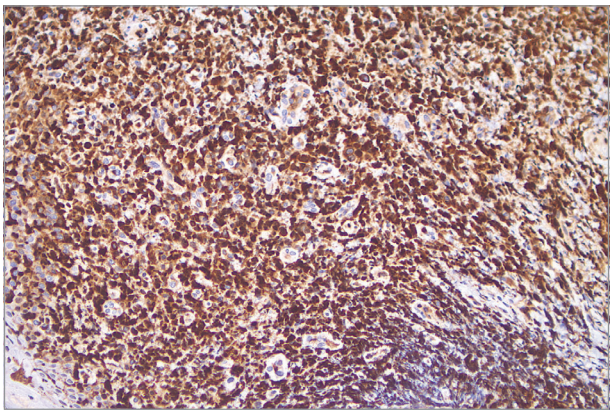

Figure 2. Granzyme B immunohistochemistry detected cytoplasmic granzyme B in atypical lymphoid cells (original magnification, ×20).

fection or squamous cell carcinoma; therefore, early biopsy is warranted when supraglottic disease persists or progresses despite appropriate antimicrobial therapy.[3]

The differential diagnosis for persistent supraglottic swelling is broad and includes bacterial epiglottitis with cellulitis or an occult abscess, laryngeal tuberculosis or fungal infection, granulomatosis with polyangiitis, and supraglottic squamous cell carcinoma. Even when purulent secretions and marked edema are present, bacterial epiglottitis typically improves rapidly with appropriate antimicrobial therapy and airway management; persistent or recurrent progression, particularly in the absence of a drainable abscess on contrast-enhanced imaging, should raise concern for a noninfectious process.[6] Laryngeal tuberculosis and certain fungal infections may cause chronic odynophagia, ulceration, and mucosal destruction that clinically and radiographically mimic cancer, but biopsy usually demonstrates granulomatous inflammation, with diagnosis supported by microbiological findings.[7] Supraglottic squamous cell carcinoma may present with ulceration or a mass and irregular enhancement on imaging, but it is an epithelial neoplasm with histopathologic and immunophenotypic features distinct from ENKTL.[1,4] Given the positive EBER and plasma EBV DNA results, other EBV-associated lymphoproliferative disorders should also be considered. EBV lymphadenitis is primarily a reactive nodal process, whereas lymphomatoid granulomatosis is typically an EBV-associated B-cell lesion.[1,8] Reported cases of acute EBV-positive cytotoxic T-cell lesions of the upper aerodigestive tract may be difficult to distinguish from ENKTL on morphologic and immunophenotypic grounds; however, these lesions rarely show angiodestructive growth, are more often seen in adolescents, tend to follow a more acute clinical course, and may undergo complete remission within a short period without radiotherapy or chemotherapy.[9]

Treatment of ENKTL depends on stage and risk stratification.[8] Because ENKTL responds poorly to anthracycline-based regimens, contemporary treatment for localized disease often integrates radiotherapy with systemic asparaginase-containing chemotherapy. For advanced-stage or relapsed/refractory disease, asparaginase-based multiagent chemotherapy may be used, and clinical trials or immunotherapy may be considered when appropriate.[10] Because laryngeal involvement may progress rapidly and threaten the airway, multidisciplinary evaluation should be initiated early once ENKTL is included in the differential diagnosis.[3]

This case report highlights an important pitfall in otolaryngology: suspected epiglottitis that fails to respond to appropriate antimicrobial therapy or follows a protracted course should prompt concern for cancer or atypical inflammatory disease and early biopsy.[6] When clinical suspicion remains high, negative or nonspecific pathology results do not exclude cancer, and repeat biopsy may be necessary.[1,4]

ARTICLE INFORMATION

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