

• Case Research •

# Synchronous occurrence of extramedullary plasmacytoma and squamous cell carcinoma in situ in the larynx: a case report

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**[Abstract]** Extramedullary plasmacytoma of the larynx is rare, especially when coexisted with squamous cell carcinoma in situ. We report a 56-year-old woman with hoarseness for 6 months and dysphonia for a week. Fiberoptic laryngoscopic examination showed a red, smooth-surface swelling in the submucous region of the left ventricle and ventricular band of the larynx. The patient underwent vertical laryngectomy and modified left neck dissection. Postoperative pathologic examination revealed coexisting plasmacytoma and carcinoma in situ. Bone marrow biopsy and systemic radiogram showed no positive findings. The hepatic and renal functions were normal. Monoclonal immunoglobulin light chain of type kappa was detected in urine. Hence, a laryngeal extramedullary plasmacytoma with carcinoma in situ was diagnosed. No recurrence or progression was observed during a 2-year follow-up. Here, we discussed the risk factors, diagnosis, and therapy for this rare disease.

**Key words:** Extramedullary plasmacytoma, larynx, head and neck, synchronous malignancy

Multiple primary malignancies were firstly described by Billoth in 1889, which are usually classified into synchronous and metachronous malignancies. Synchronous malignancies are diagnosed within six months after the first tumor is diagnosed, which have been reported to account for about 1.2% to 5.5% of all the head and neck malignancies<sup>[1-3]</sup>. Usually, patients with laryngeal cancer tend to have synchronous malignancies in the lungs, and most of the second malignancies are squamous cell carcinoma (SCC)<sup>[1]</sup>.

Extramedullary plasmacytoma (EMP), solitary plasmacytoma of the bone (SPB), and multiple myeloma (MM) constitute a continuous disease spectrum of plasma cell neoplasm caused by malignant proliferation of B lymphocytes. The first case of EMP was reported by Schridde *et al.* in 1905. EMP accounts for less than 1% of all head and neck malignancies<sup>[4]</sup>. Laryngeal EMP is a rare

solitary tumor found in soft tissues without signs of dissemination.

Synchronous laryngeal EMP and SCC in situ has not been reported before. Here, we presented such a case at our practice and discussed about diagnosis, treatment, and risk factors of this disease.

## Case Report

A 56-year-old woman was admitted to the Second Xiangya Hospital, Central South University on February 19, 2007, complaining of hoarseness for 6 months and dysphonia for 1 week. The patient denied sore throat, dysphagia, dyspnea, fever, and weight loss during the 6 months. She had no history of drinking, smoking, receiving radiotherapy and chemotherapy.

A full ear-nose-throat (ENT) examination was performed. Fiberoptic laryngoscopic examination revealed a red, smooth-surface swelling in the submucous region of the left ventricle and ventricular band of the larynx (Figure 1). No abnormality was found in the nasopharynx. Some soft lymph nodes about 1.5 cm × 0.6 cm in diameter were

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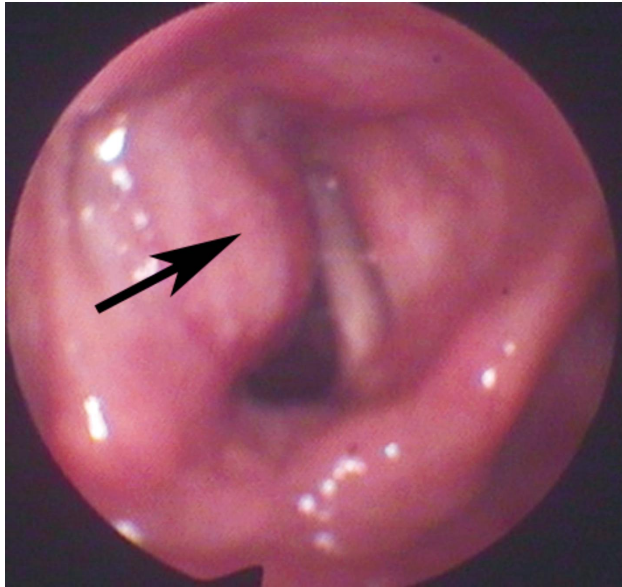


Figure 1 Fiberlaryngoscopic image of the left ventricular band of the larynx of a 56-year-old woman with hoarseness for 6 months and dysphonia for 1 week

The black arrow indicates a red, smooth-surface raised swelling in the submucous region of the left ventricle and ventricular band of the larynx. No abnormality was found in the nasopharynx.

palpated in the left side of the neck.

Contrast-enhanced computerized tomography (CT) scans showed a mass of 1.5 cm in greatest transverse diameter confined to the left supraglottic and glottic region (Figure 2). The mass had clear boundaries and heterogeneous components. The results of routine laboratory examinations, electrocardiogram, and chest radiogram were normal. Direct laryngoscopy and biopsy were performed under general anesthesia. The pathologic examination showed atypical hyperplastic squamous cells with focal carcinomatous changes.

Subsequently, the patient underwent vertical

laryngectomy and modified left neck dissection. The tumor was widely based, involving the left hemilarynx (ventricular band, ventricle, true vocal cord). Surprisingly, the pathologic examination of the resected mass showed both well differentiated plasmacytoma and poorly differentiated, atypical hyperplastic squamous cells with focal carcinomatous changes (Figure 3). Resection margins of the mass were free of tumor, and 11 cervical lymph nodes dissected from the left neck showed reactive hyperplasia. The immunostaining for CD38, CD138, epithelial membrane antigen (EMA), IgG, and IgA were positive (Figure 4), but no expression of CD20, CD3 was observed.

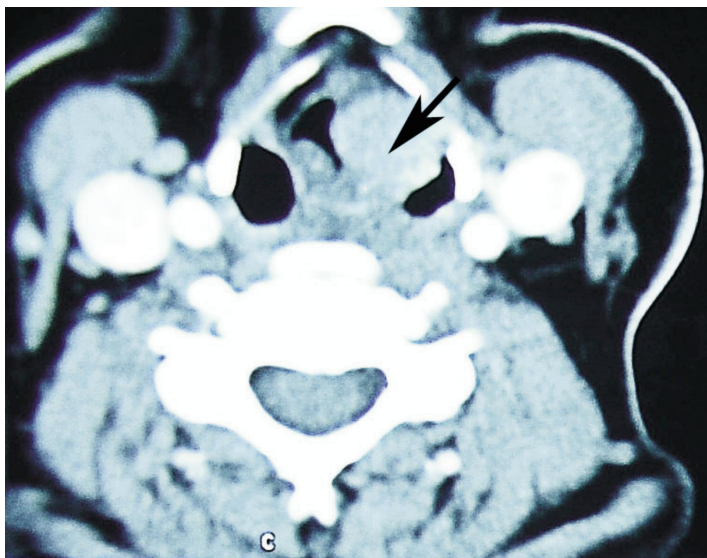


Figure 2 Axial contrast-enhanced CT scan of the larynx of a 56-year-old woman with hoarseness for 6 months and dysphonia for 1 week

The black arrow indicates a mass in the left supraglottic and glottic region with clear boundaries and heterogeneous components.

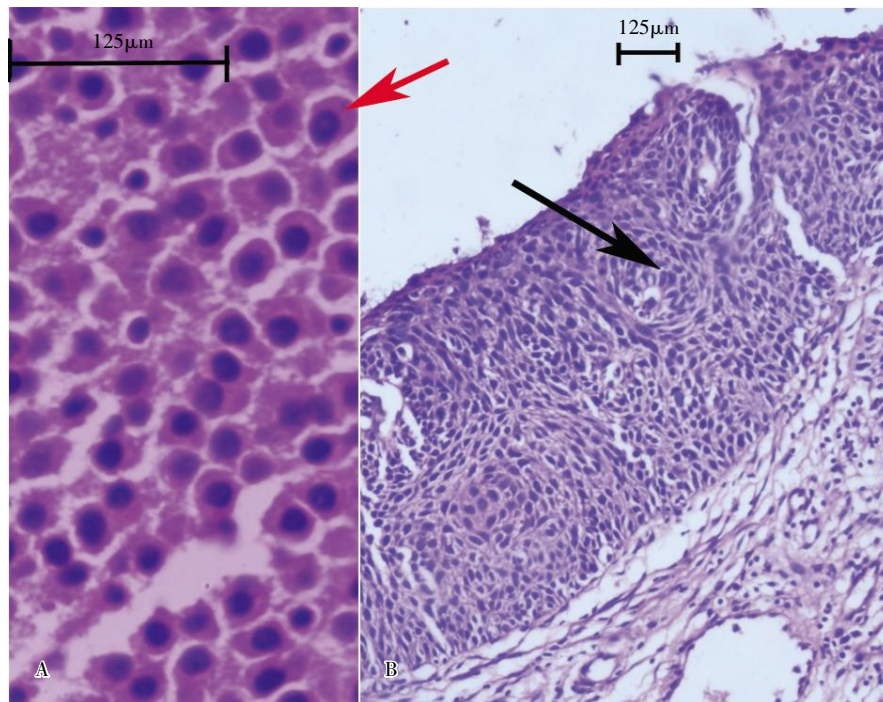


Figure 3 Pathologic examination of the resected mass from the larynx of a 56-year-old woman with hoarseness for 6 months and dysphonia for 1 week

A, mature-appearing plasma cells with eccentric, large rounded nuclei (red arrow) are observed, supporting a diagnosis of well differentiated plasmacytoma; B, atypical hyperplastic squamous cells with focal carcinomatous changes (black arrow) are observed, supporting a diagnosis of poorly differentiated squamous cell carcinoma.

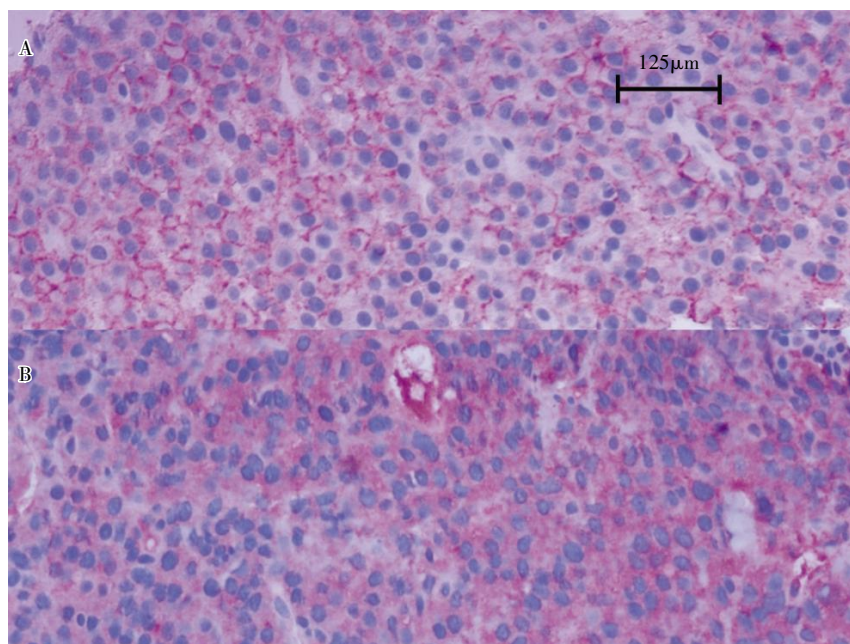


Figure 4 Immunohistochemical staining with 3-amino-9-ethylcarbazole (AEC) for the resected mass from the larynx

A, using CD138 antibody, a red precipitation in cytoplasm and on membrane of plasma cells is observed, indicating moderate expression of CD138; B, using IgA antibody, a red precipitation in cytoplasm of plasma cells is observed, indicating moderate expression of IgA.

Additional examinations for differential diagnoses of EMP and MM were performed. A biopsy of the bone marrow showed that the percentage of clonal plasma cells was less than 5% of all nucleated cells. Urine and serum protein immunoelectrophoresis detected no M protein. Radiographic skeletal surveys, abdominal ultrasonographic findings, and hepatic and renal functions were normal. The concentration of monoclonal immunoglobulin light chain of type kappa in urine was 0.09 g/L by rate immune scatter turbidimetry (reference value: 0.00 to 0.002 g/L). These results confirmed the diagnosis of laryngeal EMP and squamous cell carcinoma in situ.

Seven days after operation, the patient was extubated and discharged. The patient had been followed up every 2 to 3 months for 2 years until March, 2009. No recurrence, metastasis, or progression to MM was observed, and immunoglobulin light chain of type kappa in urine disappeared during the follow-up.

## Discussion

Synchronous malignancies in the head and neck are rare. Jones *et al.*<sup>[1]</sup> reported that only 15 (1.2%) of 1245 patients with laryngeal cancer had synchronous malignancies. Some types of lymphoma coexisting with SCC in the head and neck have been reported, such as small cell lymphocytic lymphoma, chronic lymphocytic leukemia, and diffuse large B-cell lymphoma<sup>[5,6]</sup>. However, these synchronous malignancies arose from different sites. Two different tumors affecting the same site in the larynx synchronously is extremely rare. Only one case of synchronous intravascular lymphoma and SCC in situ in the right vocal cord had been reported<sup>[7]</sup>, whereas coexisting laryngeal EMP and cancer have not been reported yet.

A few hypotheses were proposed to explain the coexistence of different tumors in the same patient. Some hypothesized that some tumors may develop simultaneously at the same site coincidentally (so-called "collision" tumors); others hypothesized that multiple tumors could arise after radiotherapy or associate with familial tumor syndromes<sup>[8,9]</sup>. Because our patient had no history of drinking, smoking, and receiving radiotherapy and chemotherapy, we speculated that the secondary tumor may be resulted from the stimulation of the first tumor, but we do not have evidence to support further discussion about pathogenesis of the coexisting tumors.

The risk factors of SCC and EMP are smoking, excessive drinking, radiotherapy, and chemotherapy. Alexiou *et al.*<sup>[10]</sup> reported radiotherapy alone tends to be a higher risk factor of progression to MM compared with surgery alone or combined therapy. Creach *et al.*<sup>[11]</sup> also reported two patients with EMP developed a radiation-induced

malignancy after radiotherapy. Besides, it was reported that the patients with an early stage (T1 and T2) tumor tend to develop a second primary tumor<sup>[1]</sup>. Moreover, supraglottic carcinoma is associated with a higher incidence of second primary malignancy<sup>[2]</sup>. Additionally, monoclonal component of EMP at diagnosis is thought to be a high risk of disease progression.

EMP accounts for about 4% of all non-epithelial tumors of the head and neck<sup>[12]</sup>, usually occurs at the age of 60s to 70s, mainly in men (man: woman ratio, from 1.4:1 to 4:1)<sup>[10,13]</sup>, and most commonly in the sinonasal region. Cady *et al.*<sup>[14]</sup> reported 2500 laryngeal malignant tumors and only one of them was plasmacytoma. About 72 cases of EMP in the head and neck were reported in Chinese literatures, and 14 of them occurred in the larynx. When the larynx is affected, EMP preferentially involves the supraglottic parts<sup>[2,15]</sup>.

The common symptoms are hoarseness, sore throat, and dysphonia, which are uncharacteristic. EMP is usually pale yellow-gray to deep red, smooth, non-ulcerated, submucous, widely based or slightly raised. The diagnosis is mainly based on histopathologic and immunohistochemical examinations. Histopathologically, EMP is composed of plasma cells with abnormal, large, round to oval nuclei surrounded by a characteristic paranuclear clearing, and with nuclear chromatin arranged in a whorl. Binucleate and pleomorphic cells with giant nuclei and prominent nucleoli are scattered in poorly differentiated EMP. Immunohistochemically, these plasma cells may express monoclonal immunoglobulin light chain of type kappa or lambda in cytoplasm; IgG and IgM appear more frequently than IgA, IgD, and IgE; immunostaining is usually positive with CD38 and CD138 antibodies and negative with CD3 and CD20 antibodies. The results of bone marrow biopsy, radiographic skeletal surveys, and laboratory examinations for EMP are normal. The patients with EMP have normal liver and renal functions, and have no symptoms of anemia and hypercalcemia. All these findings will help to rule out MM. The differential diagnosis between EMP and MM at indolent course mainly depends on the findings of bone marrow biopsy when the results of other examinations are normal<sup>[16]</sup>. Serum or urinary M component is slightly increased in less than one third of patients at initial examination. Bence-Jones protein may not be detected in urine.

Histological and immunohistochemical examinations are necessary to differentiate EMP from other tumors with plasma cell infiltration. Firstly, EMP must be distinguished from plasma cell variant of inflammatory pseudotumors (also called plasma cell granuloma or plasma cell pseudotumor). EMP usually presents with uniform-appearing cells and light chain restriction. Plasma cell granuloma is composed of plasma cells with benign proliferation,



lymphocytes, and other inflammatory cells, arising in response to an infectious or noninfectious antigenic stimulus and expressing polyclonal immunoglobulin. EMP also needs to be differentiated from other lymphomas, such as extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type. Unlike EMP, MALT lymphoma presents with viral infection and reactive proliferation of lymphoid follicles around malignant cells. In addition, immunohistochemical staining of MALT is usually positive for CD20 and Bcl-2 antibodies and negative for CD38 and CD138 antibodies, whereas EMP is usually positive with CD38 and CD138 antibodies and negative with CD3 and CD20 antibodies.

Surgery is the optimum therapy for laryngeal SCC in situ. EMP is featured by well differentiation, low proliferation, and radiosensitivity; therefore, it can be treated by radiotherapy and surgery alone or in combination. The major treatment of EMP is undetermined yet. The efficacies of surgery and radiotherapy alone or in combination are similar<sup>[17]</sup>. Soutar *et al.*<sup>[18]</sup> recommended 40 Gy irradiation by 20 fractions for EMP of up to 5 cm and a higher dose of up to 50 Gy irradiation by 25 fractions for bulky EMP of greater than 5 cm. Radiotherapy with a median dose of 50 Gy could achieve a local control rate of 95% for EMP<sup>[19]</sup>. Distant metastasis and local recurrence can be controlled by surgery and radiotherapy alone or in combination. Radiotherapy is recommended for the patients who have advanced disease and underwent surgery, or for those with unresectable EMP. On the other hand, surgery is an alternative of radiotherapy for the patients with larger lesions, severe mechanical obstruction, or tumor residue after radiotherapy. Liu *et al.*<sup>[20]</sup> believed that adjuvant radiotherapy is unnecessary for patients who have undergone complete tumor resection with negative margins. The role of adjuvant chemotherapy in treating EMP has not been reported. Applying chemotherapy for the patients with progressive disease or radiotherapy resistance is widely accepted. We recommend surgery alone for the patients with resectable tumor and without lymph node metastasis.

The prognosis for patients with EMP and SCC is favorable. The 10-year survival rate of the EMP patients without dissemination was 70% to 78%<sup>[21,22]</sup>. But because lymphoma and SCC are aggressive, especially higher grade and larger tumors, the recurrences occur mostly within the first 2–3 years after diagnosis<sup>[1,3,17,19]</sup>. There is no standard follow-up schedule for patients with EMP. Clinical symptoms of EMP progression include bone pain, fever, hemorrhage tendency, and recurrent infection. If progression to MM is suspected, bone marrow biopsy should be performed for early diagnosis. We followed up the patient every 2 to 3 months and performed detailed head and neck examination, endoscopy, serum and urine analysis, systemic radiogram, and abdominal ultrasonography. No recurrence or

progression to MM was observed, and immunoglobulin light chain of type kappa in urine disappeared. However, Bachar *et al.*<sup>[23]</sup> reported that recurrence or progression to MM may occur even decades after the initial diagnosis. Thus, we recommend a lifetime follow-up with thorough examinations.

## Conclusion

Laryngeal EMP with SCC in situ is extremely rare. Symptoms of EMP or SCC in situ include hoarseness and/or dysphagia for a short time. Endoscopy will be helpful and tumor biopsy is essential for diagnosis. The diagnosis of the coexisting tumors mainly depends on pathologic and immunohistochemical findings. We recommend surgery alone for patients with resectable tumor and no lymph node metastasis. The prognosis for patients with EMP and carcinoma in situ is relatively favorable. Lifetime follow-up is necessary to early identify local failure, progression to MM, distant metastasis, and the development of multiple malignancies.

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