

Extramedullary plasmacytoma of the larynx: Literature review and report of a case who subsequently developed acute myeloid leukemia

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Abstract. Extramedullary plasmacytoma (EMP) of the larynx is an extremely rare plasma cell neoplasm outside of the bone marrow, which has not been previously well characterized. A case of laryngeal EMP who developed acute myeloid leukemia (AML) following treatment is described in the present study, as well as an extensive review of the relevant literature. An electronic literature search was performed in PubMed and all pertinent case reports and series in the English language from 1948-October 2017 were identified. A total of 99 cases including the present case were available for review. The mean age of the included patients was 53 years. Supraglottis was the most frequently involved site. The most common treatment modality was radiotherapy alone (n=41; 43%), followed by a combination of surgery and radiotherapy, then surgery alone. However, for cases published in recent years, the most common treatment modality was surgically based treatment. Overall the treatment outcome was favorable, as a total of 84% of patients were alive after a mean follow-up of 60 months. However, EMP outcomes for patients with cervical lymphadenopathy or multiple sites involvement were unfavorable with >40% of patients relapsing or developing metastasis during the limited follow-up period. A total of 6 subjects developed multiple myeloma and 1 patient converted to AML. The present study provides important insights on the treatment of EMP, which is a rare disease. To the best of our knowledge, this is the first

case report of a patient with laryngeal EMP who developed AML following treatment. It is recommended that secondary myeloid neoplasm should be considered besides multiple myeloma during the follow-up period.

Introduction

Extramedullary plasmacytoma (EMP) is rare, accounting for approximately 3% of all plasma cell neoplasms. Up to 80% of EMP cases occur in the head and neck region, particularly in the upper aerodigestive tract, which constitutes less than 1% of head and neck tumors (1,2). Most head and neck EMPs occur in the sinonasal region, and fewer are found in the larynx (3,4). Although the primary cause of mortality is actually progression to multiple myeloma (MM), conversion to MM is uncommon (11-30% incidence). Here, we describe an individual with laryngeal EMP who developed acute myeloid leukemia (AML), rather than MM. Due to the rarity of this tumor, most previous studies focused on a case or case series. In an effort to describe this rare tumor accurately, we made a literature review about its clinical features, diagnosis, treatment modalities, outcomes, and potential sequelae of this disease.

Materials and methods

Literature review. An electronic literature search was performed in PubMed using the following terms 'plasmacytoma', 'extramedullary plasmacytoma', 'plasma cell tumor' in combination with the terms 'larynx or head and neck'. Articles published from January 1948 to October 2017 were reviewed to identify cases of laryngeal EMP. Nonhuman, duplicates, and non-English language research were excluded. Abstracts were first reviewed to screen articles that discussed cases of laryngeal EMP, and then full-text articles were reviewed for extraction of data. References of the included studies were also examined for additional cases. Individual patient data were collected on age, sex, presentation, site of lesions, treatment course, long-term follow-up and outcomes. Meanwhile, articles for which individual patient data was not available or which focused solely on radiologic, histopathological findings, and diagnosis, were also excluded.

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Abbreviations: EMP, extramedullary plasmacytoma; MM, multiple myeloma; AML, acute myeloid leukemia; t-AML, therapy-related acute myeloid leukemia; MN, myeloid neoplasm; t-MNs, therapy-related myeloid neoplasms

Key words: extramedullary plasmacytoma, larynx, treatment modality, outcomes, sequelae, acute myeloid leukemia, multiple myeloma

Statistical analysis. All the recorded treatment modalities are classified in two main categories: Surgically based treatment including surgical resection either alone or with adjuvant radiotherapy, and no-surgically based treatment. Differences between the above two treatment modalities were analyzed by chi-square test. SPSS version 20 statistical software (IBM Corp., Chicago, Illinois) was used, and $P < 0.05$ was considered to indicate a statistically significant difference for all tests.

Ethics statement. This study was approved by the ethics committee of the Second Xiangya Hospital, Central South University (Changsha, China). Written informed consent was obtained from the patient.

Results

The initial database search yielded 2,022 studies. The articles that were in non-English language, animal research, or duplicate articles were excluded, and 270 studies were left. Next, those unrelated abstracts such as solely focusing on imaging examination or histopathological findings were eliminated, and a total of 127 articles were left for further analysis. The articles in which full-text was unavailable or individual data was incomplete were ruled out. The bibliographies were also examined for additional cases. Finally, 70 studies comprising a total of 98 cases were left for analysis. Therefore, a total of 99 unique patients including our case were identified and the individual patient data collected are given in Table I (5-71). The clinical characteristics for the 99 patients included were summarized in Table II.

Case presentation. A 46-year old male presented to our hospital with cough and sore throat of a 4 month duration. He had a history of hypothyroidism for more than 10 years and received a diagnosis of tuberculosis before presenting to our hospital, but his symptoms persisted after anti-tuberculosis treatment. Fiberoptic laryngoscopy showed swelling of the epiglottis and aryepiglottic fold (Fig. 1). Laboratory findings showed an increased erythrocyte sedimentation rate, other examinations such as anti-tuberculosis antibody test and rheumatoid factors were normal. Chest X-ray was normal. Computed tomography (CT) and magnetic resonance imaging (MRI) of the neck revealed substantial swelling and edema of the epiglottis and enlargement of cervical lymph nodes. Biopsy of these two sites was performed under general anesthesia and microscopic observation showed many well-differentiated plasma cells and lymphocytes infiltration (Fig. 2). Immunohistochemical staining of the laryngeal specimen showed the most cells were positive for CD79a, CD138, CD38, CD5, Ki67, and Lambda, whereas negative for CD20, CD3, CD45RO, Cyclin D1, and PAX-5. Immunohistochemical staining of the cervical lymph nodes showed the most cells were positive for CD38, CD138, CD79a, CD45RO, CD31, Ki67, CD68 and LgG. Gene rearrangement studies indicated monoclonal rearrangements of the immunoglobulin heavy chain. A diagnosis of EMP of the larynx was made and a series of examinations were performed to exclude MM. Laboratory examinations including blood protein electrophoresis, serum immunoglobulins, urinary tests for Bence-Jones proteins were normal. Report of bone marrow biopsy was also within the normal range. In addition

to cervical lymphadenopathy, PET-CT and other imaging examinations such as CT and MRI of the chest, abdomen and pelvis showed no distant metastasis. Complete surgical resection was not suitable for this patient, so, he was referred to the Hematology-Oncology Department, and received radiotherapy including 25 sessions of 55 Gy for laryngeal lesion and cervical metastasis. Meanwhile, adjuvant chemotherapy was also given with thalidomide, vincristine, epirubicin, and cyclophosphamide. His symptoms disappeared after treatment and he had monthly follow-ups.

Five years later, he was readmitted with dizziness that lasted 2 weeks. Complete blood count showed white blood cell $1.94 \times 10^9/l$, red blood cell $1.90 \times 10^{12}/l$, haemoglobin 66 g/l, platelet $16 \times 10^9/l$. Bone marrow aspiration revealed a hyperplastic marrow: The granulocytes accounted for 29%, and the myeloblasts accounted for 12.5%; the mononocytes accounted for 32%, and the monoblasts and promonocytes accounted for 21% (Fig. 3). The blasts were positive for myeloperoxidase stain, and positive for nonspecific esterase, which was inhibited by sodium fluoride. Immunophenotyping of the bone marrow indicated that a group of blast cells (accounting for 4.84%) were positive for CD13, CD34, CD117, HLA-DR and negative for CD7, CD10, CD15, CD19, CD20, CD22, CD33, CD11b, CD14, CD64; another group of blast cells (accounting for 53.6%) were positive for CD13, CD33, CD15, CD64, CD11b, and weak positive for CD10 and CD14. These data are consistent with AML French-American-British (FAB) classification M4 subtype. Chromosome karyotype was 46, XY. Then CAG chemotherapy (aclerubicin hydrochloride, low-dose cytarabine and granulocyte colony-stimulating factor) combined with decitabine were administered accordingly and his condition alleviated. This patient is still being followed.

Patient demographics. We found greater higher occurrence in men and this was approximately two times more often than in women. The vocal cords and epiglottis are commonly involved and the main symptom is hoarseness often accompanied by dyspnea, dysphagia, and other symptoms. Supraglottic EMP accounted for the majority of patients with cervical lymphadenopathy. Likely this is due to association with lymphatic vascularity in the supraglottis, which is much denser than in the glottis or subglottis, and this causes greater incidence of lymph node metastasis.

Treatment options. Of 96 recorded treatment modalities, radiotherapy alone was the most common treatment modality, used in 41 cases, followed by a combination of surgery and radiotherapy, and surgery alone. Furthermore, we found that surgically based treatment was the most common treatment modality for cases published in recent years (Table III), despite there was no statistically significant difference between surgically based treatment and no-surgically based treatment modalities reported in these annual intervals ($P = 0.65$).

Outcomes and sequelae. Overall treatment outcome was favorable, as a total of 84% of patients were alive after a mean follow-up of 60 months, independent of treatment modality. However, EMP outcomes for patients with cervical lymphadenopathy or multiple sites involvement were unfavorable, more than 40% with recurrence or metastasis

Table I. List of laryngeal EMP cases included in analysis.

Author, year	No/sex/age	Primary sites	Treatment	LR or MET	Follow-up	Outcome	(Refs.)
The present case	1/M/46	Epiglottitis and aryepiglottic fold	RT + CT	AML	61 ms	AWD	
Pino <i>et al</i> , 2015	2/M/65	Left false cord and ventricle	S + RT	N	54 ms	ANED	(5)
Wang <i>et al</i> , 2015	3/M/43	Glottis, supraglottitis, and subglottitis	S	MM	88 ms	AWD	(6)
Haser <i>et al</i> , 2015	4/M/72	Bilaterally vocal cords and subglottitis	RT	N	1 y	ANED	(7)
Xing <i>et al</i> , 2015	5/F/47	Left aryepiglottic fold	S + RT	N	18 ms	ANED	(8)
Abrari <i>et al</i> , 2014	6/M/56	Right vocal cord	RT	N	NA	ANED	(9)
Loyo <i>et al</i> , 2013	7/F/80	Right glottis	S	NA	NA	ANED	(10)
Ghatak <i>et al</i> , 2013	8/F/29	True vocal cord	RT	N	16 ms	ANED	(11)
Kim <i>et al</i> , 2012	9/M/58	Left arytenoid	S	N	2 ys	ANED	(12)
Pinto <i>et al</i> , 2012	10/F/49	Left false fold	S	N	1 y	ANED	(13)
Ramírez-Anguiano <i>et al</i> , 2012	11/M/57	Right subglottis	S + RT	Y	1 y	ANED	(14)
De Zoysa <i>et al</i> , 2012	12/F/62	Left true vocal fold	RT	N	2 ms	ANED	(15)
Pichi <i>et al</i> , 2011	13/M/73	Left glottis and subglottitis	RT	MM	2 ys	DOD	(16)
Zhang <i>et al</i> , 2010	14/W/56	Left false vocal cord and ventricle	S	N	2 ys	ANED	(17)
González Guijarro <i>et al</i> , 2010	15/M/11	Right hemilarynx	S + RT	N	3 ys	ANED	(18)
Van an <i>et al</i> , 2009	16/F/16	Right vocal cord	RT	N	1 y	ANED	(19)
Pratibha <i>et al</i> , 2009	17/M/49	False vocal cord, vocal cord	RT	N	6 ms	ANED	(20)
Iseri <i>et al</i> , 2009	18/F/46	Aryepiglottic fold	S + RT + CT	N	2 ys	ANED	(21)
Rutherford <i>et al</i> , 2009	19/F/13	Subglottitis, nasopharynx	S + RT	N	6 weeks	ANED	(22)
Ozbilen Acar <i>et al</i> , 2008	20/F/43	True vocal cord	S	N	2 ys	ANED	(23)
Straetmans and Stokroos, 2008	21/M/57	Epiglottitis	S + RT	Y	27 ms	ANED	(1)
Velez <i>et al</i> , 2007	22/M/64	Right hemilarynx	S + RT	N	3 ys	ANED	(24)
Kusunoki <i>et al</i> , 2007	23/F/76	Supraglottitis	Biopsy	N	6 ms	AWD	(25)
Lewis <i>et al</i> , 2007	24/M/71	Supraglottitis, soft palate	S	N	2 ys	ANED	(26)
Nakashima <i>et al</i> , 2006	25/M/39	Left arytenoid	S + RT	N	6 ys	ANED	(27)
	26/M/59	Epiglottitis	S	N	15 ys	ANED	
Sakiyama <i>et al</i> , 2005	27/F/47	Subglottitis, the chest wall	RT + CT	N	7 ys	ANED	(28)
Chao <i>et al</i> , 2005	28/M/60	Supraglottitis	RT	N	37 ms	DOC	(29)
Yavas <i>et al</i> , 2004	29/F/43	Left vocal cord, nasopharynx	RT	NA	NA	NA	(30)
Michalaki <i>et al</i> , 2003	30/F/46	Larynx	RT	N	49 ms	ANED	(31)
	31/M/59	Larynx	RT	N	67 ms	ANED	
Soni <i>et al</i> , 2002	32/M/65	Subglottitis	RT	N	2 ys	ANED	(32)
Kamijo <i>et al</i> , 2002	33/M/84	False vocal fold	S + RT	N	2 years	ANED	(33)
Strojan <i>et al</i> , 2002	34/M/65	Left false vocal cord	RT	N	7.8 years	DOC	(34)

Table I. Continued.

Author, year	No/sex/age	Primary sites	Treatment	LR or MET	Follow-up	Outcome	(Refs.)
Strojan <i>et al</i> , 2002	35/M/72	Right true vocal cord	S + RT	N	4.7 ys	DOC	
Nagasaka <i>et al</i> , 2001	36/F/50	Right glottis	RT	N	2.2 ys	ANED	
Maheshwari <i>et al</i> , 2001	37/F/12	Right subglottis	S + RT	N	4 ys	ANED	(35)
Uppal and Harrison, 2001	38/M/65	Subglottis	RT	N	12 ms	ANED	(36)
Rakover <i>et al</i> , 2000	39/M/54	Left hemilarynx	RT	MM	weeks	DOD	(37)
Hotz <i>et al</i> , 1999	40/M/38	Right true vocal fold	S + RT	N	3 ys	ANED	(38)
Alexiou, 1999	41/NA/63	Larynx, nasopharynx, nasal fossa	S + RT	N	108 ms	ANED	(39)
	42/NA/45	Larynx, nasopharynx	S + RT	Y	108 ms	AWD	
	43/M/69	Larynx	S	N	62 ms	ANED	(3)
Nowak-Sadzikowska and Weiss, 1998	44/M/40	Aryepiglottic fold	S + RT	N	20 ms	ANED	
	45/M/34	Supraglottis	RT	N	10 ys	ANED	(40)
	46/M/50	Glottis	RT	N	10 ys	ANED	
	47/M/36	Supraglottis	RT	N	10 ys	ANED	
	48/F/68	Supraglottis	RT	N	10 ys	ANED	
	49/M/48	Glottis	RT	N	10 ys	ANED	
Bhattacharya <i>et al</i> , 1998	50/F/49	Supraglottis	Biopsy	N	6 ms	DOC	(41)
Sulzner <i>et al</i> , 1998	51/M/49	Right aryentoid	RT	N	5 ys	ANED	(42)
Susnerwala, 1997	52/F/79	Larynx	RT	N	132 ms	ANED	(2)
	53/M/65	Larynx	RT	N	52 ms	ANED	
Rolins <i>et al</i> , 1995	54/M/43	Epiglottis	S	N	3 ys	ANED	(43)
Mochimatsu <i>et al</i> , 1993	55/M/42	Epiglottis	S + RT	MM	12 ys	DOD	(44)
Weissman <i>et al</i> , 1993	56/M/76	Subglottis	S + RT	NA	NA	NA	(45)
Barbu <i>et al</i> , 1992	57/M/69	Supraglottis	RT	N	3 ys	ANED	(46)
Kost <i>et al</i> , 1990	58/M/43	Left vocal cord	RT	NA	NA	NA	(47)
Gambino, 1988	59/M/47	Epiglottis	S + RT	NA	NA	NA	(48)
Gaffney <i>et al</i> , 1987	60/M/80	Larynx	RT	N	7 ms	ANED	(49)
Burke <i>et al</i> , 1986	61/M/53	Supraglottis, and mouth	CT	N	1 y	ANED	(50)
Gadomski <i>et al</i> , 1986	62/F/54	Bilateral true vocal cords	S + CT	N	15 ys	DOC	(51)
	63/F/51	Right aryepiglottic fold	RT	N	5 ys	ANED	
Maniglia and Xue, 1983	64/F/64	Hemilarynx	S + RT	N	1 y	DOC	(52)
Bjelkenkrantz <i>et al</i> , 1981	65/NA	Right false vocal cord, left tonsil	S + RT	N	7 ys	ANED	(53)
Bush <i>et al</i> , 1981	66/F/52	Epiglottis, supraorbital region	RT	N	3 ys	DOC	(54)
	67/F/34	Larynx	S + RT	Y	5.9 ys	ANED	
Singh, <i>et al</i> 1979	68/F/42	Supraglottis	S + RT	N	29 ms	ANED	(55)

Table I. Continued.

Author, year	No./sex/age	Primary sites	Treatment	LR or MET	Follow-up	Outcome	(Refs.)
Woodruff <i>et al.</i> , 1979	69/F/64	Supraglottis	RT	N	6.5 ys	DOC	(56)
	70/F/34	Supraglottis	RT	N	Recently	ANED	
Petrovich <i>et al.</i> , 1977	71/M/74	Epiglottis	RT	N	6 ys	ANED	(57)
Gorenstein <i>et al.</i> , 1977	72/M/58	Right true vocal cord	S + RT	N	3 ys	ANED	(58)
	73/M/63	Right true vocal cord	S + RT	N	25 ys	ANED	
	74/M/59	Subglottis	S	N	5 ys	DOC	
	75/M/32	Subglottis	S	N	10 ys	ANED	
	76/M/42	Bilateral true cords	S	N	5 ys	ANED	
	77/M/61	Supraglottis	RT	N	6 ys	ANED	
Muller and Fisher, 1976	78/M/44	Supraglottis	Biopsy	NA	NA	AWD	(59)
Fishkinand Spiegelberg, 1976	79/M/74	Right epiglottis	RT	Y	4 ys	AWD	(60)
Stone and Cole, 1971	80/M/67	Left false vocal fold	RT + CT	N	10 ms	ANED	(61)
Poole and Marchetta, 1968	81/M/41	Larynx, multiple sites at autopsy	S + RT	Y	3 ys 5 ms	DOD	(62)
Webb, 1962	82/M/62	Left supraglottis, soft palate	RT	MM	10 ys	DOD	(63)
	83/F/55	Right vocal cord and ventricle	S	N	11 ys	ANED	
	84/M/32	Subglottis	S + RT	N	10 ys	ANED	
Dolin and Dewar, 1956	85/M/74	Larynx	RT	N	3.5 ys	DOC	(64)
	86/M/73	Larynx	S	N	1 y	ANED	
	87/M/59	Larynx	RT	N	4 ys	ANED	
Priest, 1952	88/M/50	Larynx, pharynx, and nose	S	Y	4 ys	AWD	(65)
Ewing and Foote, 1952	89/M/76	Larynx	RT	N	6 ms	AWD	(66)
Costen, 1951	90/M/52	Left epiglottis	RT	MM	1 y	AWD	(67)
Rawson <i>et al.</i> , 1950	91/F/59	Larynx	S + RT	Y	11 ys	AWD	(68)
Stout and Kenney, 1949	92/M/46	Left epiglottis, oropharynx	S	Y	14 ys	ANED	(69)
	93/F/67	Epiglottis	RT	Y	6 ms	DOD	
	94/NA	Larynx, nasopharynx and conjunctiva	S	Y	3 ys	AWD	
	95/M/64	Larynx, nasopharynx	S	Y	2 ys	AWD	
	96/F/48	Larynx, nasopharynx, and nasal cavity	S	Y	11 ys	AWD	
Hodge and Wilson, 1948	97/M/53	Left false vocal cord	S	N	1 y	ANED	(70)
Lumb and Prossor, 1948	98/M/34	Larynx	RT	Y	30 ms	AWD	(71)
	99/M/20	Larynx, palate, and tongue	S + RT	Y	7 ys 6 ms	AWD	

EMP, extramedullary plasmacytoma; M, male; F, female; RT, radiotherapy; S, surgery; CT, chemotherapy; LR, Local recurrence; MET, metastasis; MM, multiple myeloma; AML, acute myeloid leukemia; ys, years; ms, months; AWD, alive with disease; ANED, alive, no evidence of disease; DOD, died of disease; DOC, died of other causes; Y, yes; N, no; NA, not acquired.

during the limited follow-up period. A total of 21 patients were reported with relapse or metastasis in the clinical course, among which 12 cases were reported that EMP occurred in either multiple sites of the larynx or coexistence with other body sites, and 6 with cervical lymphadenopathy. A total of 6 cases developed MM finally, of which 3 cases occurred in the multiple sites of the larynx, and 2 originated in the supraglottis at the initial visits.

Discussion

EMP of the larynx is an extremely rare plasma cell neoplasm which constitutes less than 0.2% of the malignancies in the larynx (3,4). EMP may occur in various sites of the larynx such as the epiglottis, vocal folds, and subglottis. Clinical symptoms are closely related to the location of tumor and the degree of impairment of laryngeal structure. Laryngeal EMP may present different morphologic forms, sometimes a single, smooth polypoid mass, and sometimes diffuse swelling tissue just like our patient. So it is easily misdiagnosed due to the fact that the clinical symptoms and laryngoscope findings are nonspecific compared with other diseases such as laryngeal lymphoma and tuberculosis. Recently, imaging examination has been used more and more widely. For example, CT and MRI of neck may be used to identify the location of tumor and cervical lymphadenopathy, evaluate the involvement of the adjacent structures and curative effect. PET-CT has been used more and more to understand the nature of the lesion and the existence of the distant metastasis. Although radiological findings have acquired much achievement, diagnosis of EMP mainly relies on histopathologic examination by the presence of monoclonal plasma cell hyperplasia. However, the diagnosis could not be made early sometimes by routine pathological observation alone. Thus, immunohistochemistry and immunophenotype are proposed to make a definitive diagnosis or differential diagnosis, for example, most cells may be positive for CD138, CD38, CD79a, and negative for CD20, CD3 (3,4,35). Sometimes, immunoglobulin gene rearrangement analysis is also advised to confirm the diagnosis of EMP.

Given that EMPs are radiosensitive, radiotherapy is traditionally used as first-line treatment for solitary EMP (72). Similarly, single-modality radiotherapy was the most common treatment modality for laryngeal EMP, followed by a combination of surgery and radiotherapy, and surgery alone in our analysis. Recently, surgically based treatment, including surgical resection either alone or with adjuvant radiotherapy was proposed and proved that it could offer better survival outcomes compared to radiotherapy alone (3,73). In contrast, some studies showed no survival benefit for one treatment modality over another, and even recommended that radical surgery should be avoided for EMP (74). So far, the optimal treatment modality for the management of EMP remains controversial. But it has been generally accepted that chemotherapy is not considered to be a first-line therapy option and adjuvant chemotherapy is usually used in patients with disseminated or recurrent disease, that resembles the present case (3,72).

In our review, we found radiotherapy alone was the most common treatment modality for cases published between 1990 and 1999, but for cases reported from 2010 and onward, the

Table II. Clinical features of included cases.

Characteristics (n=95)	Measure, n (% total)
Patient age, mean, median (range), years	53.3, 54 (11-80)
Male, mean (n=65)	54.9
Female, mean (n=30)	50
Symptoms (n=67)	
Hoarseness	46 (69)
Dysphonia	7 (10)
Dyspnea	13 (19)
Dysphagia	9 (13)
Stridor	6 (9)
Cough	6 (9)
Sore throat	3 (4)
Hemoptysis	3 (4)
Laryngeal foreign body sensation	3 (4)
Laterality (n=41)	
Right	19 (46)
Left	17 (41)
Both	5 (12)
Primary site (n=79)	
Glottis	19 (24)
Supraglottis	41 (52)
Epiglottis	12 (15)
Aryepiglottic fold	4 (5)
Arytenoid	3 (4)
False vocal cord	8 (10)
Multiple sites	2 (3)
Unknown detailed site	12 (15)
Subglottis	10 (13)
Hemilarynx or 2-3 parts of the larynx	9 (11)
Cervical lymph nodes involvement (n=12)	
Glottic patient	1 (8)
Supraglottic patient	8 (67)
Hemilaryngeal patient	1 (8)
Coexistence with other body sites involved	17
Treatment (n=96)	
Radiotherapy alone	41 (43)
Surgery alone	21 (22)
Chemotherapy alone	1 (1)
Surgery and radiotherapy	28 (29)
Radiotherapy and chemotherapy	3 (3)
Surgery and chemotherapy	1 (1)
Radiotherapy, surgery, and chemotherapy	1 (1)
Radiotherapy dose, mean, median (range), Gy	49.6, 50 (30-70)
No treatment (n=3)	
Follow-up, mean, median (range), ms (n=90)	60, 45 (1.5-300)
Recurrence or metastasis	21 (23)
No recurrence or metastasis	69 (77)
MM	6 (7)
AML	1 (1)

Table II. Continued.

Characteristics (n=95)	Measure, n (% total)
Outcome (n=91)	
ANED	63 (69)
AWD	13 (14)
DOD	6 (7)
DOC	9 (10)

ms, months; MM, multiple myeloma; AML, acute myeloid leukaemia; ANED, alive, no evidence of disease; AWD, alive with disease; DOD, died of disease; DOC, died of other causes.



Figure 1. Fiberoptic laryngoscopic view at first presentation.

most common treatment modality was surgically based treatment. There may be some reasons for the shift toward surgical management of small tumors. On the one hand, surgical techniques advance such as laser excision application for laryngeal microsurgery has made it possible to completely resection of lesion through minimally invasive surgery. On the other hand, patients receiving radiotherapy for head and neck EMP had a higher conversion to MM (3), and we found 4 of 6 patients that developed MM received radiotherapy alone in our review, therefore, surgical management of laryngeal EMP should be considered to avoid risk factors for conversion. However, whether it could offer better survival outcomes compared to radiotherapy alone is still to be further studied. Furthermore, patient outcomes may be associated with tumor distribution or cervical lymphadenopathy in addition to treatment modality. For example, more than 40% of patients with cervical lymphadenopathy or multiple sites involvement were reported with recurrence or metastasis, or even died of disease in our review. In summary, patient outcomes may be affected by many aspects, and management of laryngeal EMP should also be considered on a case-by-case basis. **Factors such as tumor location; histological grade; regional lymphadenopathy; feasibility of complete resection; laryngeal function; and potential risk of recurrence or conversion to MM should be considered when determining the most suitable treatment modality.**

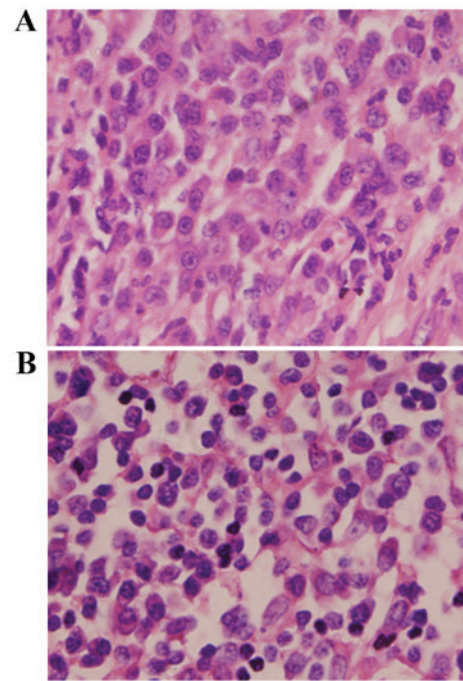


Figure 2. Histopathological examination of the biopsy specimens. Pathological findings revealed a large amount of plasmacyte and lymphocyte infiltration in the (A) laryngeal tumor tissue and (B) cervical lymph nodes (haematoxylin and eosin staining, magnification, x400).

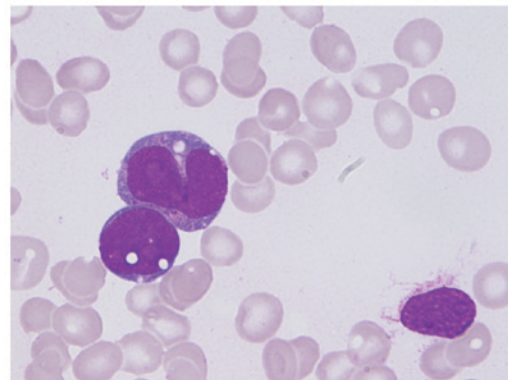


Figure 3. Bone marrow aspirate smear revealed myeloid leukemia cells (Wright-Giemsa staining, oil immersion lens; magnification, x1,000).

EMPs tend to have more favorable outcomes than solitary bone plasmacytomas or MM, and overall survival for 10 years is estimated to exceed 70% (73). We noted that 84% of patients in our analysis were alive after a mean follow-up of 60 months. However, we also found that patients with cervical lymphadenopathy, multiple anatomical regions of the larynx or other organ involvement may be prone to relapse or metastasis. The highest risk of conversion to MM is reported to be in the first 2 years after diagnosis, but conversion has also been noted more than 15 years later (4). In our analysis, 3 patients developed MM in the first 2 years, and 1 subject developed MM 12 years later. Although there is debate about high risk factors of conversion to MM, once converted to MM, patients have poor prognosis, and fewer than 10% of patients survive 10 years (3). Therefore, progression to MM maybe a poor prognostic factor or a

Table III. Treatment modalities by annual interval.

Treatment modality	Years			
	1948-1989	1990-1999	2000-2009	2010-2017
Surgically based treatment (%)	22 (55)	7 (41)	11 (46)	9 (60)
No-surgically based treatment (%)	18 (45)	10 (59)	13 (54)	6 (40)

determinant factor for survival. Few patients developed MM in our analysis, and this was less than the expected range. This may be due to the relatively short follow-up for most cases. Therefore, follow-up and regular screening for MM is important.

To the best of our knowledge, this is the first case of laryngeal EMP who subsequently developed AML. On one hand, AML, as the primary second tumor, may occur subsequent to plasma cell myeloma or MM. On the other hand, the occurrence of AML in this case maybe closely related to chemotherapy or radiotherapy, and so it is referred to as therapy-related AML (t-AML). At this time, it is unclear whether this represents an intrinsic predisposition or therapy-related phenomenon (75). Similarly, the pathologic procedure and pathogenesis for this case are unclear and must be elucidated. Even so, this unusual case provides evidence that laryngeal EMP may develop therapy-related myeloid neoplasms (t-MNs) even though this is rare.

In conclusion, we present a comprehensive literature review spanning 60 years to increase awareness of laryngeal EMP. Our findings suggest radiotherapy alone is the most common treatment modality, but surgically based treatment has been the most common treatment modality in recent years. EMP localized to a single region of the larynx may have good outcomes. In addition to MM, t-MNs should be considered during the follow-up period. Due to the inherent limitations of this review, further study about optimal treatment modalities should be considered with randomized controlled clinical trials.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

YY conceived this study, interpreted the results and revised the manuscript. SG analyzed the literature data and wrote the manuscript. GZ performed the data collection and analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Second Xiangya Hospital, Central South University and written informed consent was obtained from the patient.

Patient consent for publication

Written informed consent was obtained from the patient consent for the publication of their data and associated images.

Competing interests

The authors declare that they have no competing interests.

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