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*Case Report*

# Gingival extramedullary plasmacytoma converted to multiple myeloma: a case report and systematic review of the literature

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**Abstract:** Plasma cell tumors are lymphoid malignancies characterized by uncontrolled proliferation of B cells. Localized forms of this tumor are defined as extramedullary plasmacytoma and solitary bone plasmacytoma while multiple myeloma is defined as the disseminated type. A 70-year-old female presented with a swelling on the left cheek for more than 3 years. Physical examinations revealed a mass in intraoral gingiva on the left upper mandible. Computed tomography displayed pleural effusion, abnormal soft tissue density masses around spine and ribs, behind sternum and above adrenal glands as well as an osteolytic lesion in the body of several vertebrae. The biopsy in the gingival and post-sternal masses revealed plasmacytoma and bone marrow aspiration confirmed plasma cell infiltration (>10%). A diagnosis of multiple myeloma (StageI) converted from an initial gingival extramedullary plasmacytoma was established. The patient subsequently received 2 cycles of VAD regimen chemotherapy and the symptoms were temporarily relieved. We performed systematic reviews of literature and provided a meta-analysis of the frequency of extramedullary plasmacytoma progression to multiple myeloma. Both primary gingival extramedullary plasmacytoma and multiple myeloma with the first presentation in gingival are extremely rare, and yet for this case, we diagnosed as a primary gingival extramedullary plasmacytoma that had progressed to multiple myeloma.

**Keywords:** Extramedullary plasmacytoma, multiple myeloma, gingiva, pleural effusion

## Introduction

As a lymphoid neoplasm of B cells, plasma cell myeloma presents as one of the three following types: multiple myeloma, solitary plasmacytoma of bone, and extramedullary plasmacytoma [1]. Extramedullary plasmacytoma and solitary bone plasmacytoma are localized forms of this neoplasm while multiple myeloma is the disseminated type [2]. According to the updated criteria by International Myeloma Working Group [3], the diagnosis of multiple myeloma requires clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of myeloma-related clinical signs. If clonal plasma cells are absent in bone marrow, it is classified as solitary plasmacytoma, while if the percentage of bone marrow plasma cells is less 10%, it is called plasmacytoma with low marrow involvement. The common clinical complications attributed to myeloma include hypocalcaemia, renal insufficiency, anemia, and bone lesions while solitary plasmacytomas, present solely in bone or soft tissue mass and are often localized without systematic complications [4]. Compared with multiple myeloma, extramedullary plasmacytomas could be well controlled by surgery or (with) chemotherapy and promise a better survival period, nevertheless, some extramedullary plasmacytomas do progress to multiple myeloma.

Here, we report an extremely rare and interesting case, which presented multiple myeloma accompanied by abundant pleural effusion that was putatively converted from an initial gingival extramedullary plasmacytoma. The detailed

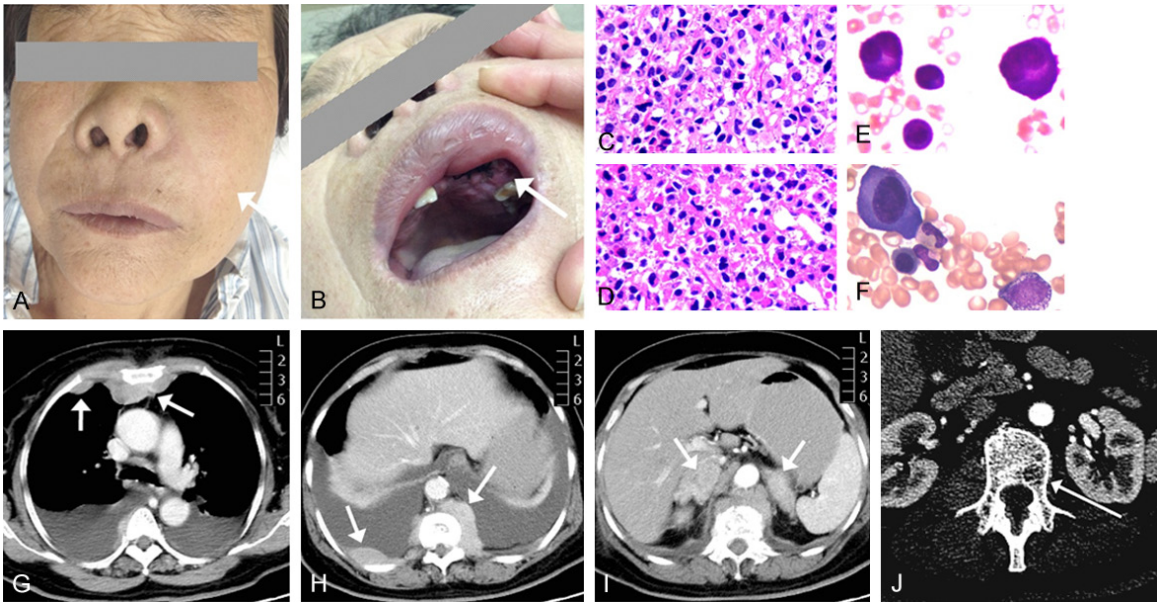


**Figure 1.** Clinical manifestations of the neoplasm. Patient pictures showing the left cheek swelling (A) and gingival mass (B). Pathology analysis revealed plasmacytoma in gingival mass (C) and post-sternal mass (D). Plasmacytoma cells were detected in pleural effusion (E) and bone marrow (F). CT scans showing pleural effusion (G, H) and abnormal soft tissue density mass (white arrow, G-I) and a typical osteolytic lesion in vertebra (J).

discussion of this case was based on systematic review of literature about this rare condition.

## Case Presentation

A 70-year-old Chinese female was referred to our department with a swelling on the left cheek for more than 3 years (**Figure 1A**). The swelling dramatically enlarged in recent 3 weeks and became painful accompanied by dyspnea, right hip pain, and approximately 5 kilograms' loss in body weight. Physical examinations revealed a mass in the intraoral gingiva on the left upper mandible with tenderness (**Figure 1B**), and signs of abundant pleural effusion.

Computed tomography (CT) displayed: (1) a 3.5×3.0×2.0 soft tissue density mass in the gingiva on the left upper mandible; (2) pleural effusion (**Figure 1G**, **1H**); (3) extensive abnormal soft tissue density mass around the spine and the ribs, behind the sternum and above the adrenal glands (**Figure 1G-I**); (4) a sporadic osteolytic lesion in the body of several vertebrae (**Figure 1J**). Results of blood cell counts, urine routine and erythrocyte sedimentation rates were all within normal ranges while comprehensive biochemistry showed slightly elevated ALT (44 u/l) and AST (82 u/l) as well as dramatically elevated LDH (601 u/l). A tumor marker panel revealed elevated level of CA-125 (123.80 u/m), NSE (61.86 ng/ml), and SCC (1.8 ng/ml), while CEA, CYFRA21-1, and CA-199 level remained in the normal range.

A primary carcinoma or sarcoma in the gingiva with multiple metastases was initially suspected for this patient, however, biopsy and histopathology analysis both in the gingival mass and the post-sternal mass revealed plasmacytoma (**Figure 1C**, **1D**). Consistently, abundant abnormal plasma cells were found in the pleural fluid after thoracentesis (**Figure 1E**). Subsequent bone marrow aspiration confirmed bone marrow plasma cell infiltration for this patient (**Figure 1F**). Serum immunofixation electrophoresis showed a monoclonal protein [IgGtype] (2.16 g/l) with elevated β2-microglobulin (2.89 mg/l) but Bence-Jones protein was negative in the urine.

Based on serum monoclonal protein, bone marrow monoclonal plasma cell infiltration (>10%) and typical osteolytic lesion in the vertebra, a diagnosis of multiple myeloma (Stage I) was established and the patient was then transferred to the Department of Hematology for further treatment. The symptom of dyspnea

**Table 1.** Reported cases of gingival primary plasmacytoma in literature

| Publication year | Age | Gender | Primary manifestations | Treatment | Progression |
|---|---|---|---|---|---|
| 1968 [32] | 16 | M | The gum grew gradually and constantly without pain along the lower canines for about one year and gingivitis involving both jaws | Gingivectomy | No bone lesion was found in radiographic examination. |
| 1982 [33] | 62 | M | An asymptomatic red spongy lesion involved the labial gingiva and alveolar mucosa grew slowly for more than three years | Surgery excision | No evidence of multiple myeloma found |
| 1995 [34] | 28 | M | CyA-induced gingival overgrowth was revealed one year after renal transplantation and the lesion had increased progressively in size one year later, | Stopping the use of CyA; & immunosuppressive treatment | Local control |
| 2005 [35] | 54 | F | A painless swelling of right shoulder, and redness and swelling of gingiva six months later | Chemotherapy with vincristine, doxorubicin, and dexamethasone | No evidence of multiple myeloma found in repeat extensive workup |
| 2007 [36] | 54 | F | A purplenodule in the vestibular area of left maxillary canine for more than two months | Radiotherapy | Local control for more than 11 months |
| 2012 [37] | 65 | F | A swelling in the posterior triangle of the neck near the thoracic outlet for 4 months and a swelling in the lower left anterior gingival region below the upper maxillary canine for two months. | Refused to take any treatment. | No sign of multiple myeloma found initially. After one year, the patient developed into multiple myeloma and died 3 months later. |
| 2012 [26] | 52 | M | A painless, gingival mass for three months. | Radiotherapy followed by conditioning chemotherapy | Regression of the oral lesion |
| 2014 [38] | 65 | F | A growth in lower jaw front teeth region for four months | Some naturotherapy treatments | The patient died one year later due to cardiac arrest without progression to multiple myeloma |
| 2014 [39] | 63 | M | An evolving swelling in the maxilla with involvement of palate and gingiva for about six months | Chemotherapy with lenalidomide and dexamethasone | Recurrence of oral lesion two months later |

was relieved after bilateral pleural effusion drainage and her left cheek swelling and right hip pain was dramatically relieved after 2 cycles of chemotherapy with VAD regimen. Six months later the patient died due to respiratory failure.

## Discussion

To our knowledge, only 9 cases of primary plasmacytoma of the gingiva could be found in literature (**Table 2**) and 3 other cases presented the gingival manifestation as the first sign of multiple myeloma. These cases were rarely reported yet our case was unique among them. Thus we based our discussion on systematic review about gingival plasmacytoma and gingival presentation of multiple myeloma.

According to the data from the Surveillance, Epidemiology and End Results Program (1992-2004) [5], the incidence of multiple myeloma, solitary plasmacytoma of bone, and extramedullary plasmacytoma is 53.5, 1.5, and 1.0 per million respectively and men are predominant. Extramedullary plasmacytoma of soft tissue represents the rarest entity among plasmacytomas and it arises predominantly in the head and neck, particularly the upper aero-digestive tract [6-8]. In retrospective research based on literature review, 82.2% of extramedullary plasmacytoma was found in the upper aero-digestive tract, among which the nasal cavity or paranasal sinus was mostly involved, and the rest were commonly in the gastrointestinal tract [9].

Primary extramedullary plasmacytomas involving gingiva are extremely rare and only presented in series of case reports (**Table 1**). Gingival extramedullary plasmacytomas in the literature date back to 1964. In an early comprehensive review about extramedullary plasmacytoma in the head and neck region, at least 150 cases had been reported prior to its publication and 9 of them presented in the maxilla or gingiva, but details were not provided [8]. The reported cases in **Table 1** were summarized from a thorough search of the English literature. All of the listed 9 cases had presented a relatively long term history of oral manifestation and most of them had good local control by surgery or chemotherapy. However, it should be noted that the diagnostic criteria in the time of the early reports varied from our current system. In fact, with the development of new investigation technology, such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) [10],

**Table 2.** Summary of the rate of conversion of extramedullary plasmacytoma to multiple myeloma in the literature

| First Author | Publication year | Population | Number of extramedullary plasmacytoma cases | Progression to multiple myeloma |
|---|---|---|---|---|
| Wiltshaw, E. [40] | 1976 | British | 44 | 18 (40.9%) |
| Corwin, J. [41] | 1979 | American | 12 | 2 (16.7%) |
| Harwood, A. R. [42] | 1981 | Canadian | 14 | 2 (14.3%) |
| Bush, S. E. [43] | 1981 | Mexican | 10 | 2 (20%) |
| Kapadia, S. B. [44] | 1982 | American | 16 | 4 (25.0%) |
| Knowling, M. A. [45] | 1983 | Canadian | 25 | 2 (8%) |
| Mayr, N. A. [46] | 1990 | Canadian | 13 | 3 (23%) |
| Brinch, L. [47] | 1990 | Norwegian | 18 | 2 (11.1%) |
| Soesan, M. [48] | 1992 | Italian | 35 | 1 (2.9%) |
| Holland, J. [49] | 1992 | American | 14 | 5 (35.7%) |
| Galieni, P. [50] | 1995 | Italian | 22 | 3 (13.6%) |
| Shih, L. Y. [51] | 1995 | Chinese | 10 | 1 (10.0%) |
| Bolek, T. W. [52] | 1996 | American | 9 | 3 (33%) |
| Susnerwala, S. S. [25] | 1997 | British | 25 | 2 (8%) |
| Liebross, R. H. [53] | 1999 | American | 22 | 7 (31.8%) |
| Alexiou, C. [9] | 1999 | Germany | 7 | 0 (0%) |
| Galieni, P. [54] | 2000 | Italian | 47 | 7 (14.9%) |
| Tsang, R. W. [55] | 2001 | Canadian | 14 | 2 (14.3%) |
| Strojan, P. [24] | 2002 | Slovenia | 26 | 2 (7.7%) |
| Kremer, M. [14] | 2005 | Germany | 25 | 0 (0%) |
| Ozsahin, M. [31] | 2006 | Switzerland | 52 | 18 (34.6%) |
| Kilciksiz, S. [30] | 2008 | Turkish | 23 | 3 (13.4%) |
| Suh, Y. G. [56] | 2012 | South Korea | 16 | 3 (18.8%) |
| Baghmar, S. [57] | 2012 | Switzerland | 8 | 1 (12.5%) |
| Katodritou, E. [11] | 2014 | Greek | 32 | 5 (15.6%) |

the diagnosis of suspected solitary plasmacytoma might be modified to multiple myeloma after the sensitive assessment of systematic involvement.

Compared to solitary plasmacytoma of bone, the extramedullary plasmacytoma has a reduced chance to evolve to multiple myeloma [11, 12]. However, the precise proportion of tumor evolution was unclear, hence we provided a meta-analysis (**Figure 2**) based on the literature concerning the progression of extramedullary plasmacytoma using the extracted data in **Table 1**. The calculations and data plots were all conducted by package of "meta" written in R [13]. The rates of conversion to multiple myeloma varied from 0% to 40.9% in single study and showed great heterogeneity except in North America subgroup, which might be partly attributed to inconsistent criteria and various treatments. In the study of Kremer, M. et al. [14], none of 25 extramedullary plasmacytomas evolved to multiple myeloma and, based on immunohistochemical analysis, they found that extramedullary plasmacytoma and multiple myeloma had biological differences since the universal lack of cyclin D1 expression and the frequent absence of CD56 in extramedullary plasmacytoma. Collectively, the pooled proportion of progress was 15% in random effect model, higher in North America (18%) and lower in Europe (13% in random effect model).

One the other hand, multiple myeloma could present with extramedullary plasmacytoma, which could be achieved by local growth, hematogenous spread, or could be triggered by invasive surgical procedures [15]. In a longitudinal study including 1003 multiple myeloma patients, 13% of them had extramedullary plasmacytoma and this involvement confered a poorer prognosis [16]. In a study of 958 patients

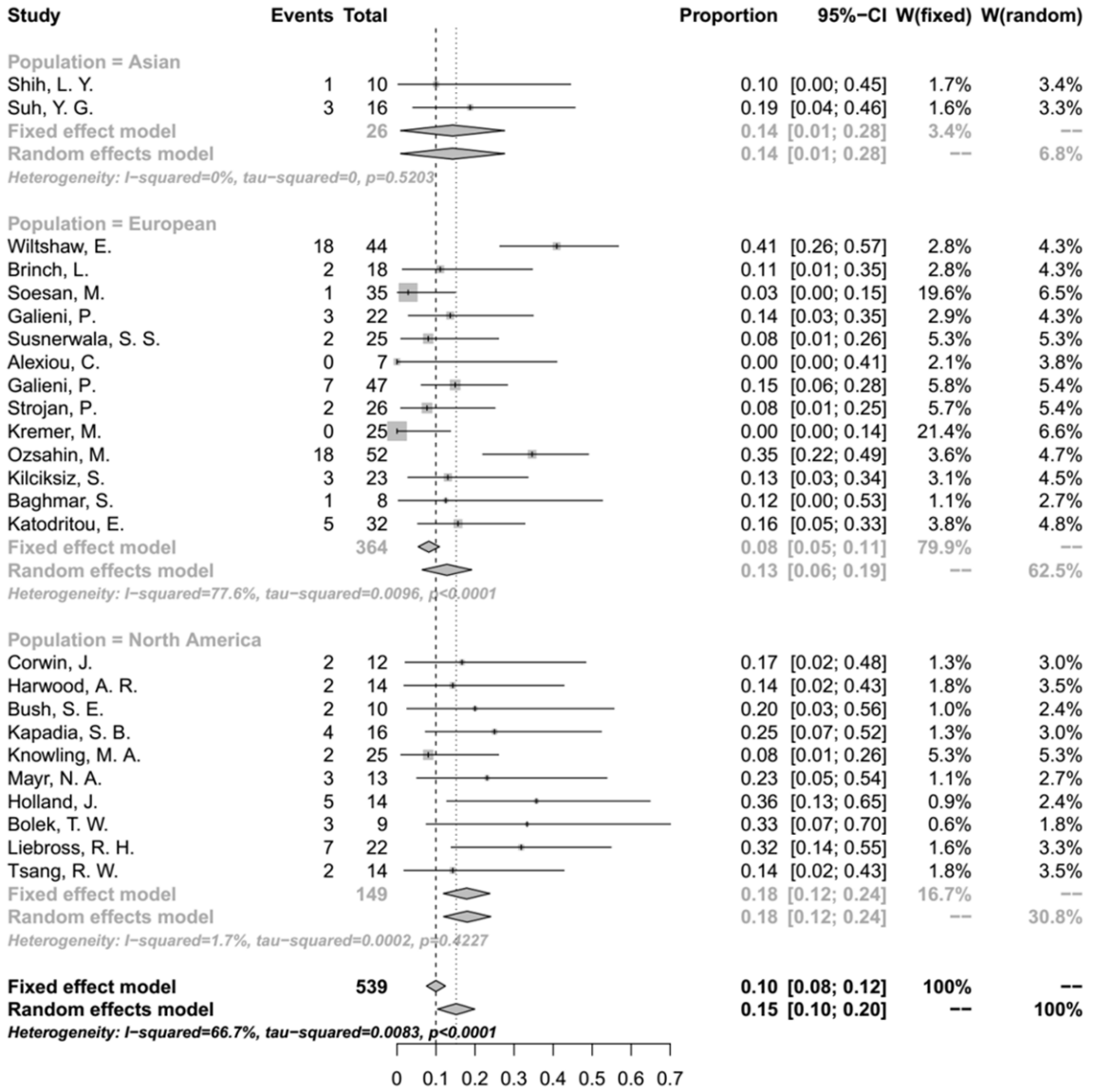


**Figure 2.** Meta-analysis of the chance of extramedullary plasmacytoma progression to multiple myeloma.

with multiple myeloma, 58 (6%) of them had pleural effusions [17]. Oral cavity involvement was more common in advanced multiple myeloma. In 1953 Bruce and Royer reviewed 59 patients with multiple myeloma and found 17 of them exhibited evidence of myeloma in the jaws, of which all but one were general skeletal involvement [18]. In 1984, Epstein et al. detected 14.1% of 783 cases of multiple myeloma presented maxillofacial manifestations [19]. Lambertenghi-Deliliers et al. evaluated a lower incidence (5.18% of 193 patients) of alterations of the maxilla and mandible in multiple myeloma [20]. The common features of the above series are that the mandible was more frequently involved than the maxilla and most patients with oral manifestation had extensive skeletal involvement [18-20].

There are few case reports demonstrating gingival manifestation as the first sign of multiple myeloma [21-23]. In the report by Lee SH et al. the first case of a 55-year-old man had a painful and progressively enlarged mass in the left lower posterior edentulous area started approximately 2 months previously, and relapsed 10 months later; the second case of 53-year-old woman had a history of bone pain for 6 months and was hospitalized for gingival swelling and bleeding in the left lower premolar

and molar area for several days [21]. The case of a 52-year-old man reported by Shah, Ajaz et al. showed a chief complaint of right sided maxillary gingival mass with hypermobility of the adjacent teeth for 10 days [22]. Dabell M. et al. presented a unique case of multiple myeloma presenting as gingival swelling with the jaw being the only bone affected at diagnosis [23]. These reported cases above all showed osteolytic lesions around their gingival mass, indicating a local growth of the neoplasm from the jaw bone instead of hematogenous spread.

Compared with cases of gingival manifestation of multiple myeloma, however, our cases presented several distinct features: first, the gingival mass of our case was noticed more than two years before referral; second, no bone lesion around the gingival mass was detected in CT; finally, the biopsy results and other workup were compatible with an early stage of multiple myeloma (Stage I). Thus, we tend to consider this case as a primary gingival extramedullary plasmacytoma which evolved to multiple myeloma.

In histology, the well-differentiated plasmacytoma is featured by a homogeneous population of differentiated plasma cells [14, 24, 25]. However, the poorly differentiated plasmacytoma presents a mixture of plasma blasts, immature binucleateplasma cells, and mature plasma cells, which might be confused with plasmablastic lymphoma and their complete overlap in immunohistochemistry [26, 27]. For extramedullary plasmacytoma of the head and neck region, radiotherapy could improve its overall survival [28, 29]. According to a retrospective study of 67 patients, the 5- and 10-year disease-free survival rates of extramedullary plasmacytoma of the head and neck were 56% and 54%, respectively [29]. However, the prognosis of progressed extramedullary plasmacytoma was as poor as multiple myeloma [11, 30, 31].

## Conclusion

To summarize, we presented an unusual case of multiple myeloma and due to the long history of her gingival mass and the fact of the low chance of gingival involvement of multiple myeloma, especially for early stage multiple myeloma, we diagnosed as a primary gingival extramedullary plasmacytoma that had progressed to multiple myeloma. Our systematic literature review also provided a comprehensive and meaningful review for this field.

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Written informed consent was obtained from the son of the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

## Disclosure of conflict of interest

None.

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