# Multicentric Castleman disease detected during the evaluation of tongue cancer: A case report

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**Abstract.** Castleman disease is a non-neoplastic lymphoproliferative disorder that encompasses a variety of disease types. The current study reports a case of multicentric Castleman disease that was incidentally detected during the workup for tongue cancer. A 73-year-old male visited the Tochigi Medical Center (Utsunomiya, Japan) in May 2022, with the main complaint of pain on the left side of his tongue. At his initial visit, a 25x15 mm exophytic tumor with a slightly ambiguous border was observed on the left side of the patient's tongue. Positron emission tomography/computed tomography revealed numerous abnormal accumulations on the left side of his tongue as well as in the cervical and systemic lymph nodes. A tongue biopsy revealed a diagnosis of squamous cell carcinoma. Meanwhile, as a result of fine needle aspiration from the cervical lymph nodes and a biopsy of the inguinal lymph nodes, lymph node lesions were diagnosed to be a plasma cell variant of Castleman disease. Subsequently, a partial glossectomy was performed under general anesthesia, with the final histopathological diagnosis of the lingual lesions being squamous cell carcinoma as well. The progress of the patient was monitored since the symptoms of Castleman disease were mild and asymptomatic. At 30 months postoperatively, none of the lesions had progressed, and the postoperative course remained uneventful.

## Introduction

Castleman disease is a relatively rare non-clonal lymphoproliferative disease characterized by the histopathological findings of the lymph nodes, as reported by Castleman *et al* (1). Clinically, it is classified into unicentric Castleman disease (UCD), in which the affected lymph nodes are confined to a single region, and multicentric Castleman disease (MCD), characterized by generalized lymphadenopathy (2-5). The clinical symptoms of CD include a variety of systemic symptoms and abnormalities upon testing. CD is characterized by histological findings such as lymphoid follicle hyperplasia and vascular invasion into lymphoid follicles, and is definitively diagnosed based on histopathological findings. The most common site of Castleman disease is the mediastinum, accounting for approximately 70% of all cases; however, 15% of such cases occur in the head and neck (6). Therefore, it is necessary to keep in mind the concept of Castleman disease when cervical lymphadenopathy is observed. However, it is extremely rare for Castleman disease to occur in association with head and neck cancer cases, including oral cancer, in which case it becomes difficult to distinguish between the metastatic lymph nodes from head and neck cancer and Castleman disease. Furthermore, the treatment for the two diseases is completely different, so proper diagnosis is essential.

We experienced a case of MCD that was incidentally detected during an evaluation of tongue cancer, and report this case with a review of the pertinent literature.

## Case report

A 73-year-old male was referred to our department by our Internal Medicine Department in May 2022 under a suspicion of tongue cancer on the left side. The patient became aware of pain in the same region one month prior to his initial visit. His medical history included chronic kidney disease, hypothyroidism, chronic stasis dermatitis, and anemia. At his initial visit, a 25x15 mm exophytic tumor with a slightly ambiguous border was observed on the left side of his tongue; however, no paresthesia of the lingual nerve was observed (Fig. 1). In addition, no obvious swelling or tenderness of the cervical lymph nodes was palpable. A biopsy revealed well-differentiated squamous cell carcinoma (Fig. 2). A neoplastic lesion measuring 25x15x4 mm in size was observed on the left side of his tongue upon Computed tomography (CT) and Magnetic resonance imaging (MRI), with mild enlargement observed in the submental lymph nodes and left

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submandibular lymph nodes; however, no lung lesions were observed (Fig. 3). F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) revealed a strong accumulation of SUVmax 6.9 on the left side of his tongue. An abnormal FDG uptake was also observed in the submental lymph node (SUVmax 5.2) and the left submandibular lymph node (SUVmax 4.8) (Fig. 4). In addition, multiple intense accumulations (SUVmax 1.7-6.5) were detected in the lymph nodes of both axillae, around the abdominal aorta, in the pelvic cavity, and in both inguinal regions (Fig. 5). Blood test results indicated low values of hemoglobin content (Hb) at 10.4 g/dl and albumin (Alb) at 3 1g/dl, a slightly elevated C-reactive protein (CRP) at 1.79 mg/dl, and a high γ-globulin fraction in the protein fractionation pattern at 38.4%. Although lymphoproliferative disorder was suspected, metastasis from tongue cancer to the cervical lymph nodes could not be ruled out. For this reason, we performed fine needle aspiration (FNA) on the submental lymph nodes and left submandibular lymph nodes, while observing no atypical epithelial cells suggesting metastasis (Fig. 6). In addition, we consulted our Dermatology Department and performed a lymph node biopsy from the left inguinal region. Histologically, we observed follicle formation with an embryonic center and significant plasma cell proliferation around the follicle. When we investigated kappa/lambda chains by means of clonality studies, the plasma cells were not biased by kappa/lambda chains and immunohistochemistry did not reveal any findings that could be considered to be tumor proliferation. Since there was also no amyloid deposition, the patient was diagnosed with a plasma cell variant of Castleman disease (Fig. 7).

Based on the above, in August 2022, a left partial glossectomy was performed under general anesthesia with a diagnosis of left lingual squamous cell carcinoma (cT2N0M0, stage II) along with MCD. Following the resection, the wound was sutured with 4-0 absorbent sutures (Fig. 8). Histopathologically, the lesion showed a sheet-like proliferation of atypical squamous cells with a tendency to keratinize, thus forming large and small nests and infiltrating into the superficial muscle layer. Moreover, low-grade dysplasia was observed in the white mucosa around the tumor (Fig. 9). The depth of invasion was 2 mm and venous infiltration was observed; however, no lymphatic vessels or nerve infiltration was observed. Based on the above, the lesion was diagnosed as squamous cell carcinoma (SCC) of the tongue (pT2N0M0, grade 1, stage II). Our hematology department thereafter was responsible for the treatment for Castleman disease. Because the symptoms were mild and asymptomatic, with the 10-year survival rate expected to be 80% even without treatment, our course of action was to monitor his progress without using any immunosuppressive drugs and tocilizumab. It was decided that if symptoms such as fatigue and slight fever appeared, then the administration of 0.3 mg/kg/day of prednisolone will be initiated, and if these symptoms were to either worsen or if organ symptoms are observed, then the administration of tocilizumab would be considered while increasing the dose of prednisolone to 1 mg/kg/day. Postoperatively, the patient has been undergoing monthly follow-up visits and CT scans every three months to monitor the status of his tongue and the lymph node lesions. Currently, there has been no evidence of any recurrent metastasis of the tongue cancer even 30 months following surgery, and with no progression of Castleman disease observed.

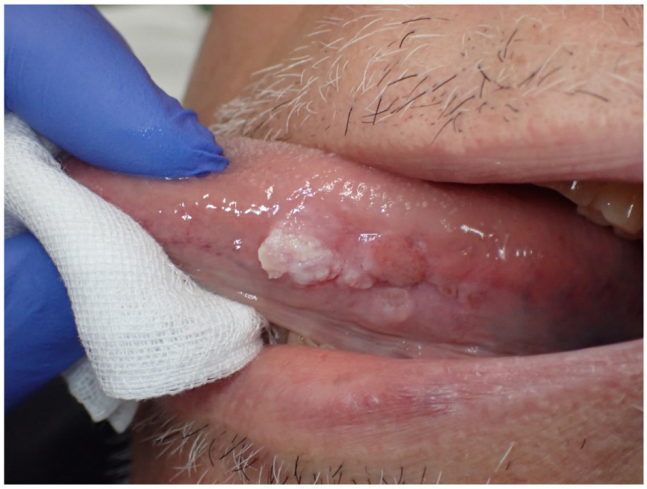

Figure 1. Intraoral findings during the initial examination. A 25x15 mm exophytic tumor with an indistinct border was observed on the left side of the patient's tongue.

## Discussion

Castleman disease is a non-neoplastic lymphoproliferative disorder of unknown origin and it is a relatively rare disease that was reported by Castleman *et al* (1) in 1956. Subsequently, it was histopathologically classified into three types by Keller *et al* (7): hyaline vascular type (HV type); plasma cell type (PC type); and mixed type (M type). HV type is histologically characterized by the proliferation of lymphoid follicles and the proliferation and vitrification of blood vessels between follicles. It has few clinical symptoms and it rarely demonstrates abnormal values upon blood testing. On the other hand, PC type is characterized by the diffuse, sheet-like infiltration of plasma cells into the interfollicular tissue and expansion of the follicular spaces, which often causes a variety of clinical symptoms such as generalized lymphadenopathy, anemia, and abnormal blood tests. Although there are no specific immunohistochemical markers for diagnosis, plasma cells may occasionally be identified using CD138 immunostaining. Moreover, depending on the distribution of the lesions, it is also distinguished from UCD, which occurs only in a single lymph node, and MCD, which spreads to multiple regions. In principle, UCD corresponds to HV type, and MCD corresponds to PC type and M type. However, typical findings are not always obtained in the histopathological diagnosis of MCD, so careful judgment is required for each individual case, while carefully considering the available clinical information. The clinical symptoms of MCD include general malaise, fever, anemia, high value of CRP, hypergammaglobulinemia, and a variety of systemic symptoms and abnormalities upon testing. A diagnosis is made based on both the clinical symptoms and the histopathology of the enlarged lymph nodes (2). While clinical symptoms such as general malaise and fever were not observed in our case, low Hb and Alb values and a high gamma-globulin fraction were observed upon blood testing. In addition, due to the fact that a CT scan confirmed the enlargement of lymph nodes across multiple regions and that the degree of plasma cell infiltration was histopathologically high, it was diagnosed as a PC type of MCD.

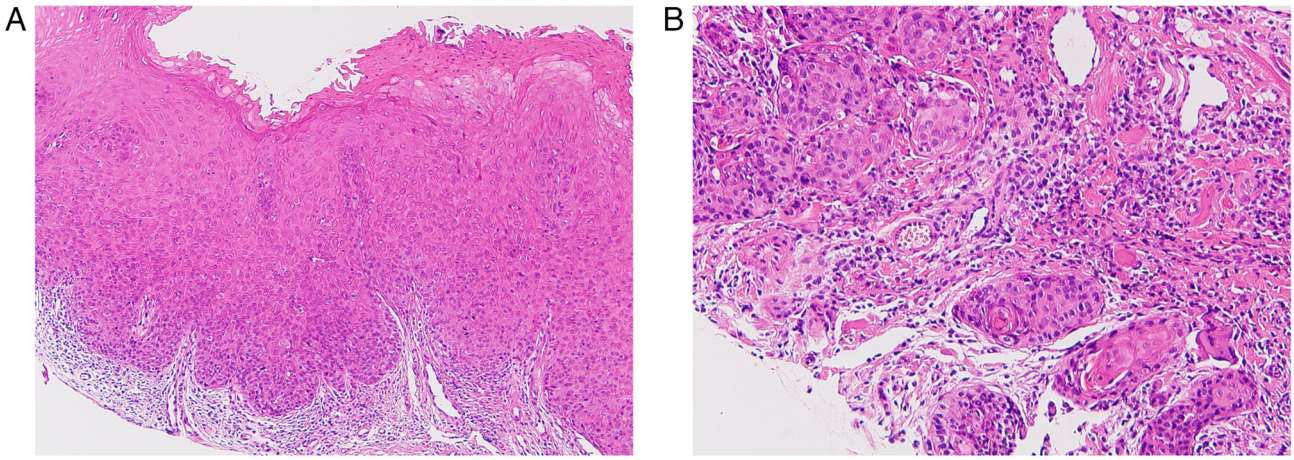


Figure 2. Histopathological findings of the tongue biopsy specimen (hematoxylin-eosin stain). (A) Magnification, x100 and (B) x200. The lesion was diagnosed as well-differentiated squamous cell carcinoma.

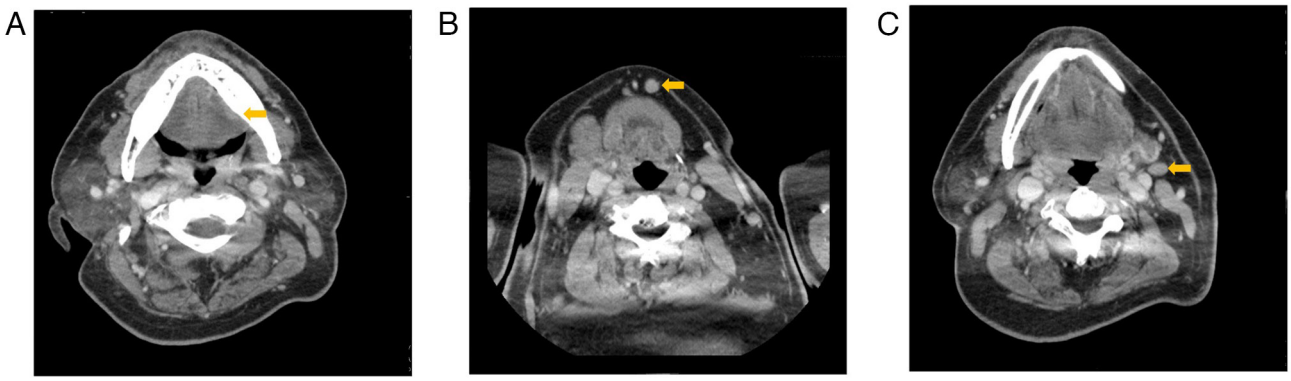


Figure 3. Contrast-enhanced computed tomography images. (A) A neoplastic lesion measuring 25x15x4 mm was observed on the left side of the tongue. Mild enlargement was observed in the (B) submental and (C) left submandibular lymph nodes.

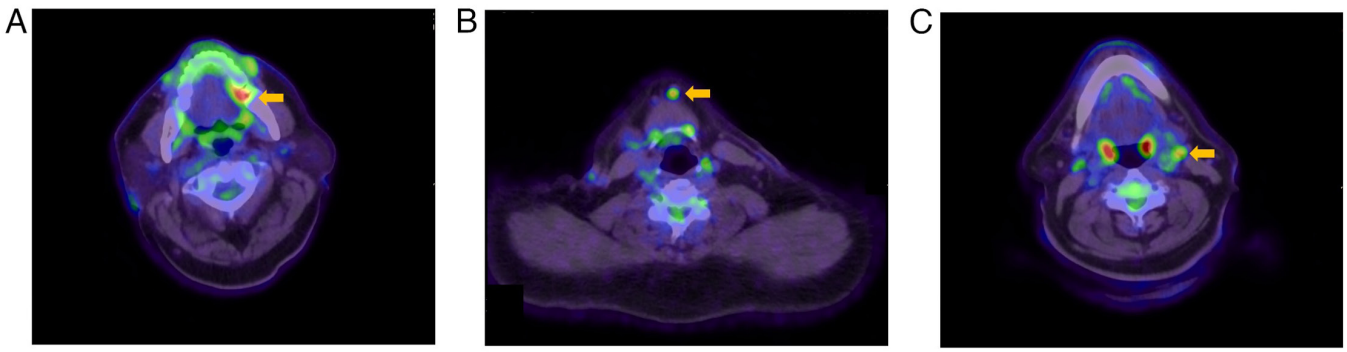


Figure 4. Positron emission tomography/computed tomography images of the neck. (A) Strong FDG accumulation was observed on the left side of the tongue. Abnormal FDG uptake was also seen in the (B) submental and (C) left submandibular lymph nodes.

While the most common site of Castleman disease is the mediastinum, 15% of such cases occur in the head and neck, and it is also known to occur in the abdominal cavity and axilla. The differential diagnosis of Castleman disease occurring in the neck includes inflammatory cervical lymphadenitis, cervical lymph node metastasis of malignant tumors, and malignant lymphoma, as well as sarcoidosis and IgG4-related diseases. If head and neck cancer is present, then cervical lymph node metastasis should first be suspected. In our case, multiple abnormal FDG accumulations were systemically observed in addition to cervical lymph nodes upon PET/CT, suggesting at least some form of lymphoproliferative disorder. However, regarding the cervical lymph nodes, because the possibility of metastasis from tongue cancer could not be ruled out, FNA was performed. As far as we were able to find, English-language reported cases of Castleman disease occurring in conjunction with head and

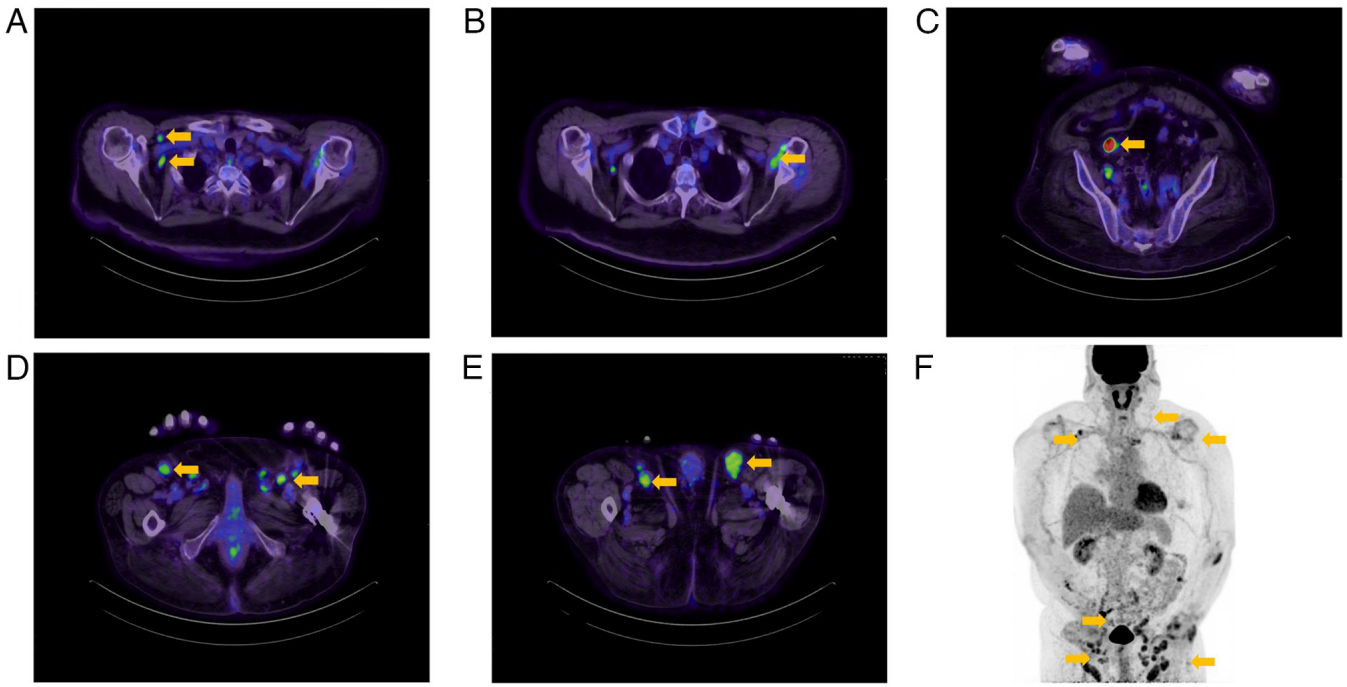


Figure 5. Positron emission tomography/computed tomography images of the trunk. (A-C) Strong FDG accumulation was observed in the bilateral axillary and intraperitoneal lymph nodes. (A) Right axillary lymph nodes. (B) Left axillary lymph node. (C) Intraperitoneal lymph node. (D and E) Abnormal FDG uptake was also seen in the bilateral inguinal lymph nodes. (F) Multiple lymph nodes showed abnormal FDG accumulation.

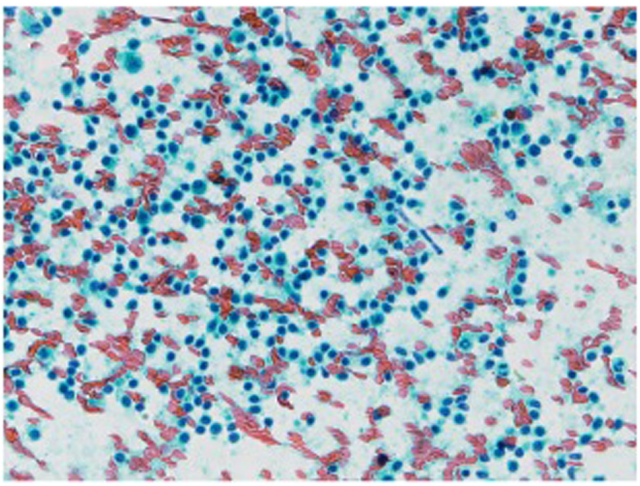

Figure 6. Fine needle aspiration cytology findings of cervical lymph nodes. Red blood cells and mature lymphocytes were found, but no atypical epithelial cells indicative of metastasis were observed. Papanicolaou staining, magnification, x400.

neck cancer are extremely rare, with only three known cases, including our own case (8,9) (Table I). The average patient age was 47.7 years, with two patients in their 30s. There were two males and one female, with the cancer site being the tongue in all three cases. Histopathologically, two cases were HV type, and one case was PC type. Regarding the site of lymphadenopathy, two cases occurred at a single site (mediastinum, submandibular region) and one case occurred at multiple sites. As noted earlier, both of the two non-self cases of UCD corresponded to HV type. Lymphadenopathy was also observed in the neck in two cases, including our own case. In one case, under a diagnosis of cT1N3aM0, hemi-glossectomy and bilateral neck dissection were performed. However, no lymph node metastasis was observed in the postoperative histopathological diagnosis, so it may have been possible to treat the disease by partial resection alone. In our own case, only a partial glossectomy was performed based on the results of the preoperative FNA. To differentiate between metastatic lymph nodes from oral cancer and Castleman disease, cervical ultrasonography, CT, and MRI are first performed. However, as both conditions present with very similar imaging findings, a definitive diagnosis requires either FNA or a biopsy of the lymph node.

MCD is believed to be caused by the sustained production of interleukin-6 (IL-6) (10). For this reason, treatment is centered on IL-6 inhibitors, with siltuximab mainly used (11); however, tocilizumab (2), an anti-IL-6 receptor antibody, is the only approved treatment by the Japanese National Health Insurance System. In asymptomatic cases with only mild laboratory abnormalities, as in the present case, careful observation may be an appropriate management option. In moderate to severe cases, the concomitant use of steroids is recommended in addition to tocilizumab (12,13). With proper treatment, the prognosis is relatively good, with a 5-year overall survival rate of 100% and a 10-year overall survival rate of 90% or more in Japan (14). That said, obtaining a complete cure is difficult, with most patients not achieving permanent remission even via treatment with tocilizumab (15), so further therapeutic drug development and clinical trials are needed going forward.

While the relationship between Castleman disease and SCC has not been clarified, the involvement of IL-6 has been suggested (16). IL-6 is a cytokine involved in a variety of biological events, including immune reactions, hematopoiesis, and acute phase reactions, with the overproduction thereof thought to be involved in the development of chronic inflammatory

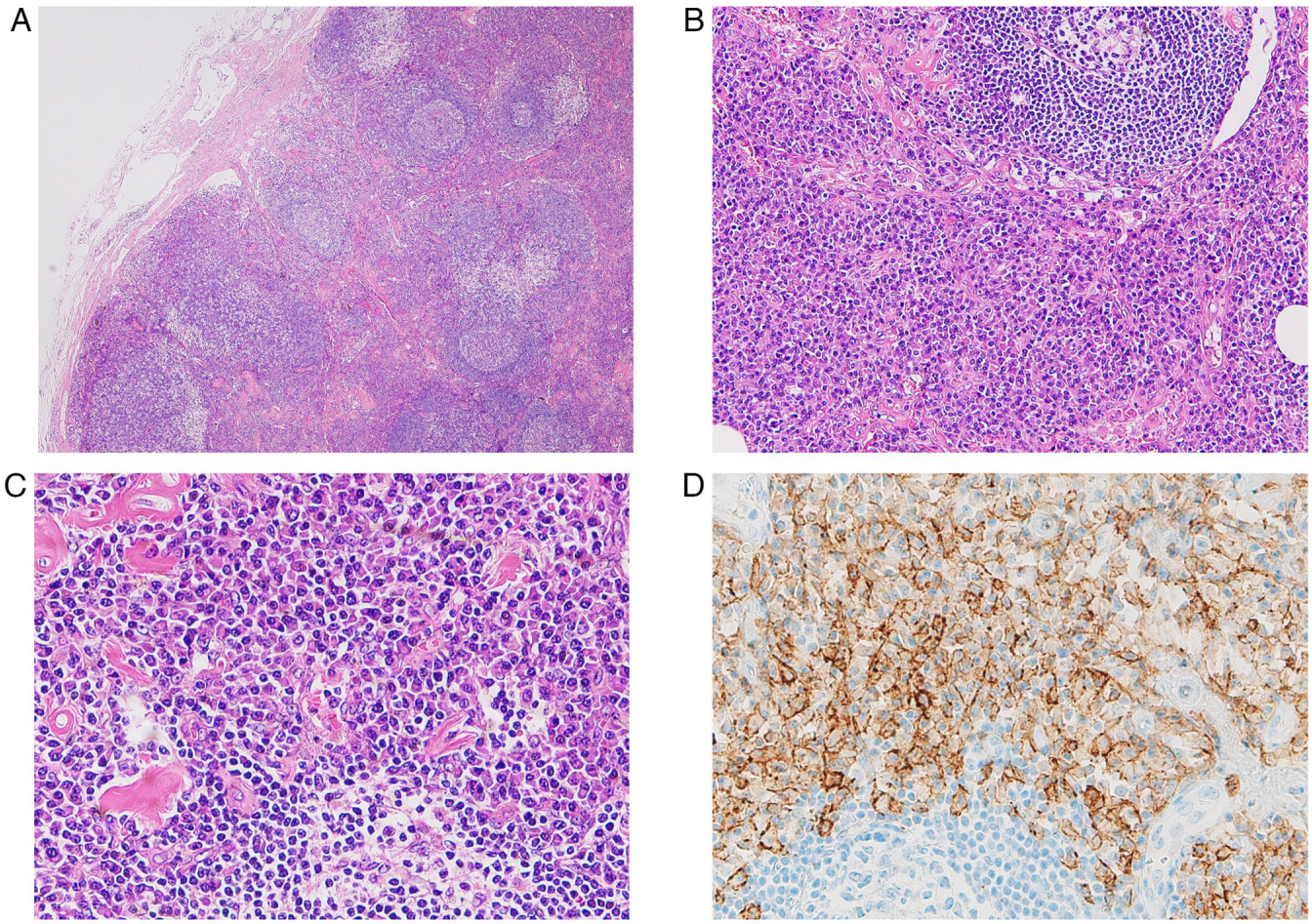


Figure 7. Histopathological findings of the left inguinal region. (A-C) Hematoxylin-eosin staining and (D) immunohistochemistry for CD138. (A) Magnification, x40. Numerous large and small lymphoid follicles were observed. (B) Magnification, x200. Marked plasma cell proliferation was seen around the follicles. (C) Magnification, x400. Diffuse proliferation of plasma cells was observed. (D) Magnification, x400. Marked CD138 expression indicates plasmacytic proliferation.

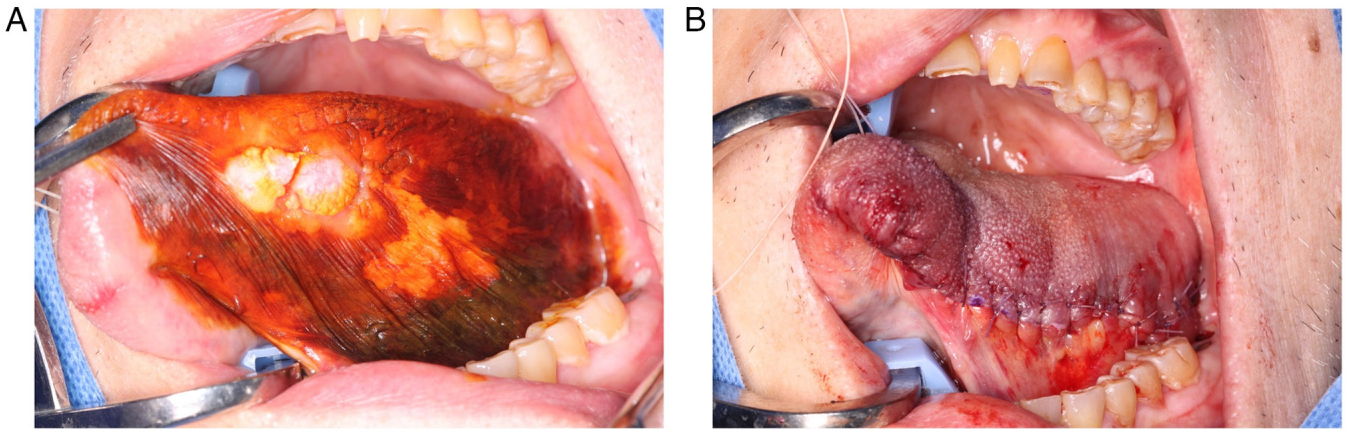


Figure 8. Intraoperative photographs. (A) After iodine staining of the lesion. (B) The surgical wound was sutured with 4-0 absorbable sutures.

diseases and cancers. Riedel *et al* (17) reported that they observed elevated serum IL-6 levels in head and neck SCCs, particularly in advanced cancers with lymph node metastases. In this case, the symptoms of Castleman disease were mild and asymptomatic, and since no active therapeutic intervention was undertaken and only observation was performed, the IL-6 levels were therefore not measured. Regarding the monitoring method, if Castleman disease and oral cancer coexist, as observed in this case, then it is necessary to confirm both lesions, with imaging examinations conducted once every 3 to 6 months considered to be appropriate. Although the course of MCD is generally slow, it is recommended to conduct systemic

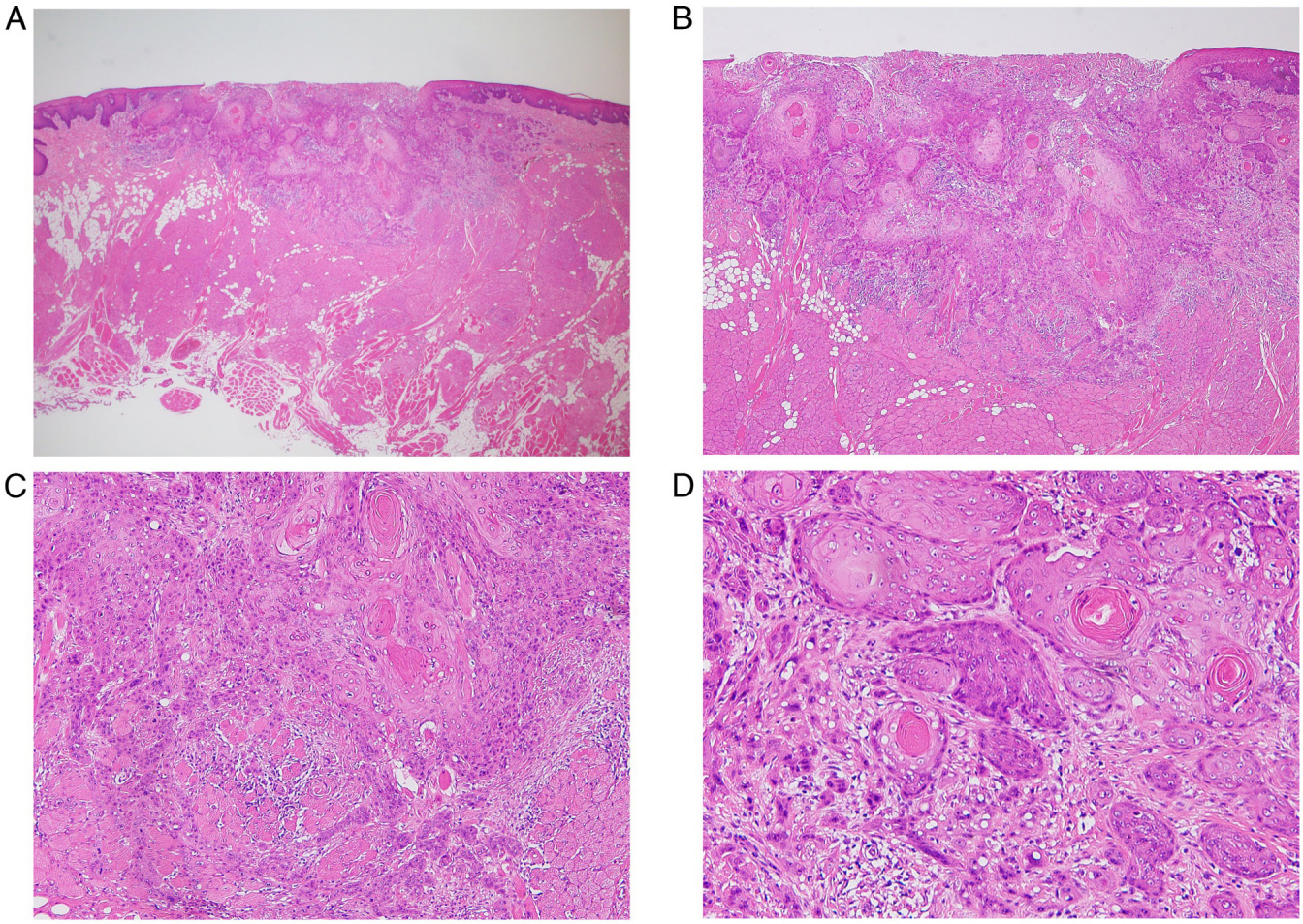


Figure 9. Histopathological findings of the resected tongue specimen (hematoxylin-eosin stain). (A) Magnification, x20, (B) x40, (C) x100 and (D) x200. The lesion showed sheet-like proliferation of atypical squamous cells with keratinization, forming large and small nests infiltrating the superficial muscle layer.

examinations such as PET/CT once a year. In addition, in conjunction with the Hematology Department, we should be prepared to respond quickly when symptoms appear.

We described a case of MCD that was incidentally detected during an evaluation of tongue cancer and reviewed the literature on this rare entity. Distinguishing between lymphadenopathy in Castleman disease and lymph node metastasis in oral cancer is difficult using just the clinical findings and images alone. In order to provide appropriate treatment, it is necessary to carry out a histopathological examination in cooperation with the relevant departments to make an appropriate diagnosis and stage classification.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

YY conceptualized the case report, performed the acquisition, analysis and interpretation of data and drafted the manuscript. YY, SS, MY, MN and KS were involved in the treatment and follow-up in this case. SA advised on patient treatment, analyzed patient data, critically revised the manuscript and provided valuable feedback, provided supervision, and approved the final manuscript for publication. YY and SA confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

The patient provided written informed consent for publication, authorizing the use of their imaging, pathological and clinical data for publication.

**Competing interests**

The authors declare that they have no competing interests.

Table I. Castleman disease occurring in conjunction with head and neck cancer.

| Author | Sex | Age | Location of SCC | Location of lymph node enlargement | Clinical diagnosis | Diagnosis at biopsy | Treatment | Histopathological diagnosis | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|
| Pereira *et al* | F | 38 | Tongue | Right posteromedial mediastinum | Germ cell cell tumor | Small blue lesion | Right posterolateral excision of chest wall and thoracotomy with the right paraspinous tumor | Hyaline vascular type Castleman disease | (9) |
| Deshmukh *et al* | M | 32 | Tongue | Submandibular lesion | Cervical lymph node metastasis | NA | Bilateral modified neck dissection | Hyaline vascular type Castleman disease | (8) |
| Present case | M | 73 | Tongue | Submental and left submandibular, bilateral axillary, abdominal periaortic, pelvic, and bilateral inguinal lymph nodes | Lymphoproliferative disorders | Plasma cell type Castleman disease | Observation | - | - |

SCC, squamous cell carcinoma; NA, not available; F, female; M, male.

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