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【 CASE REPORT 】

Successful Treatment of Incidental Histiocytic Sarcoma Concomitant with Laryngeal Carcinoma

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Abstract:
Histiocytic sarcoma (HS) is an extremely rare non-Langerhans cell disorder with an aggressive course and limited treatment options. HS most often presents at an advanced clinical stage, with a limited response to chemotherapy and high mortality. No standard treatment has been established for HS. We herein describe the first case of HS concomitant with laryngeal carcinoma that was promptly diagnosed and successfully treated; the condition of the patient has remained stable for 4 years with no recurrence.

Key words: histiocytic sarcoma (HS), laryngeal carcinoma, CHOP

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Introduction

Histiocytic sarcoma (HS) is a malignant proliferation of cells showing morphological and immunophenotypic features of mature tissue histiocytes. It occurs over a wide range of ages and shows a male predominance (1). Some cases of HS are associated with hematological disease. Lymph nodes are the most common site of presentation, although various extranodal sites, including the gastrointestinal tract, spleen, soft tissue and skin, may be affected. Histologically, the tumor shows diffuse infiltration of large, round to ovoid pleomorphic cells. Immunohistochemically, HS is identified by the expression of CD68, CD163 and lysozyme, typically with the absence of B-cell and T-cell related markers as well as dendritic cell, epithelioid and myeloid cell markers (1, 2).

HS most often presents at an advanced clinical stage, with a limited response to chemotherapy and high mortality. No standard treatment has been established for HS. Most patients die from disseminated disease within two years (3), although there are some survivors. A past report showed that the size of the tumor was an important factor affecting the prognosis and survival time of patients with a primary tumor diameter of >3.5 cm (4).

HS is rare, and no cases of incidental HS concomitant with laryngeal carcinoma have previously been reported. We herein describe a case of incidental HS that was promptly diagnosed and successfully treated.

Case Report

A 74-year-old Japanese man was referred to our hospital because of a cervical tumor that was identified on a computed tomography (CT) scan. His past medical history included pulmonary adenocarcinoma (Stage IA), which was diagnosed 28 months prior to his current presentation. The patient had been treated with right middle lobectomy, which was performed by video-assisted thoracoscopic surgery. He did not receive adjuvant chemotherapy or radiotherapy. On admission, his temperature was 36.2°C and his blood pressure was 131/64 mmHg. He had right cervical masses on palpation. Laboratory tests revealed the following: white blood cell count, 8.8×10^9/L; neutrophil count, 5.9×10^9/L; red blood cell count, 532×10^{10}/L; hemoglobin concentration, 14.2 g/dL; and platelet count, 221×10^9/L. His lactate dehydrogenase level was 208 U/L (normal range: 106-211 U/L) and his C-reactive protein level was 0.38 mg/dL (normal range: lower than 0.30 mg/dL). His soluble interleukin 2 receptor (sIL2R) level was 784 U/mL (normal range: 145-519 U/mL). A fluoro-deoxy-glucose(FDG)-positron emission tomography (PET)/CT scan revealed intense FDG uptake in

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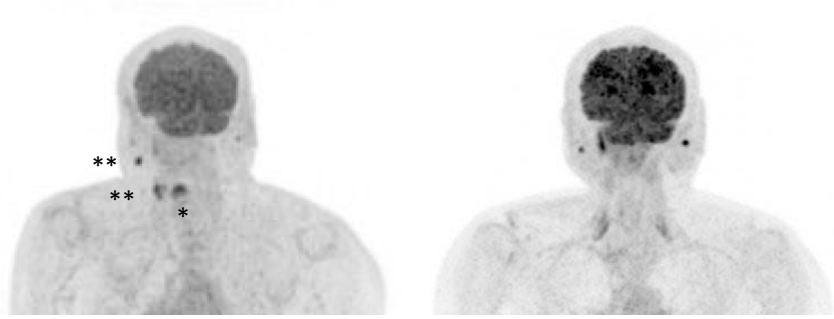

(a) (b)

Figure 1. **(a) A fluoro-deoxy-glucose (FDG) -positron emission tomography (PET)/computed tomography (CT) scan revealed intense FDG uptake in the right cervical mass (*) and lymph nodes (**). (b) After chemotherapy, the complete remission of HS was confirmed on PET/CT.**

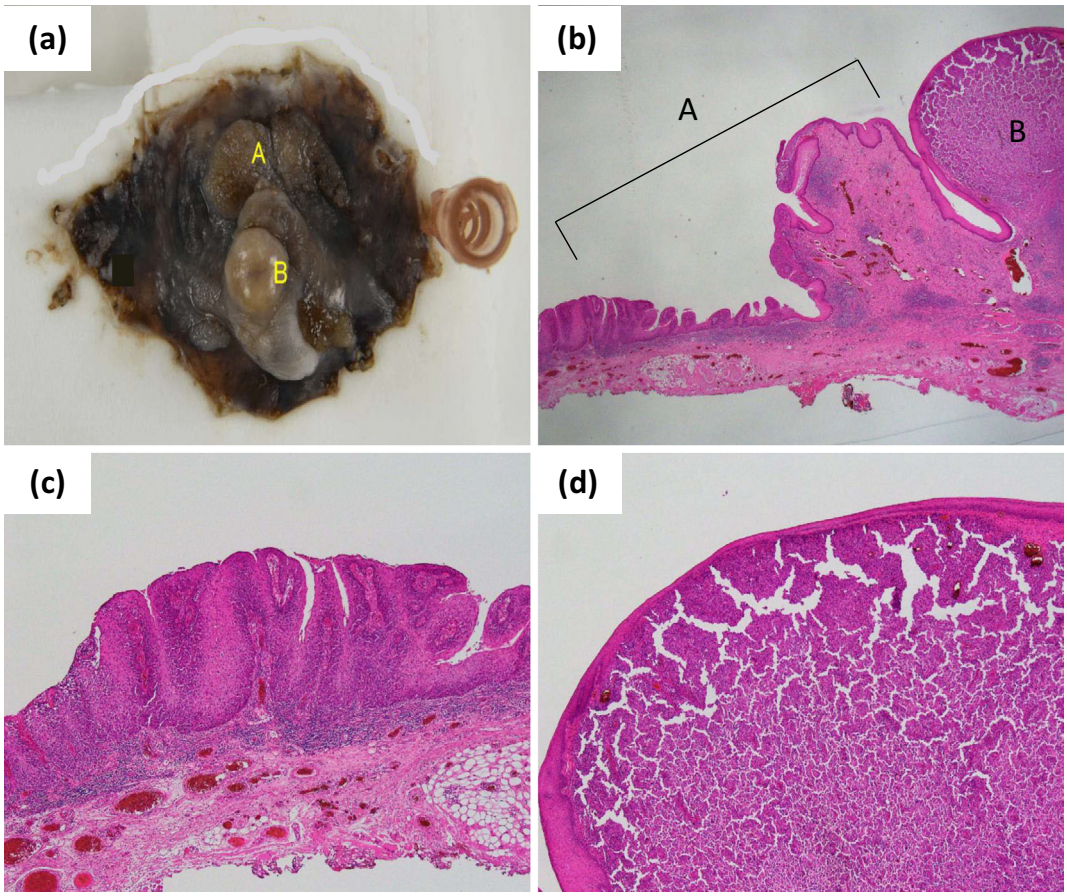

Figure 2. **(a, b) The cervical mass contained two masses: A and B. (c) Microscopic examination of mass A showed squamous cell carcinoma [Hematoxylin and Eosin (H&E) staining, ×40]. (d) Mass B showed histiocytic sarcoma (H&E staining, ×40).**

the right cervical mass (SUV-max 5.77) (Fig. 1a, *) and lymph nodes (SUV-max 4.90) (Fig. 1a, **). The patient underwent resection of the mass and lymph nodes. Two masses were present: A (16×9 mm) and B (11×8 mm) (Fig. 2a). Microscopic examination of mass A (Fig. 2b, c) showed squamous cell carcinoma, while mass B (Fig. 2b, d) showed diffuse infiltration of large and irregular pleomorphic cells with lobulated nuclei and some binucleated and trinucleated cells containing abundant blue cytoplasm (Fig. 3a). Immunohistochemistry showed the absence of B-cell, T-cell, and myeloid markers (CD45, CD3, CD79a, CD20, CD34, MPO, CD15, CD30 and CD117), as well as epithelial markers and anaplastic lymphoma kinase 1. Neoplastic cells were positive for histiocyte markers (lysozyme, CD68 and CD163) (Fig. 3b-d). The morphology and immunoprofile were consistent with the diagnosis of HS concomitant with laryngeal carcinoma. The lymph nodes showed metastatic squamous cell carcinoma. DNA was extracted from formalin-fixed

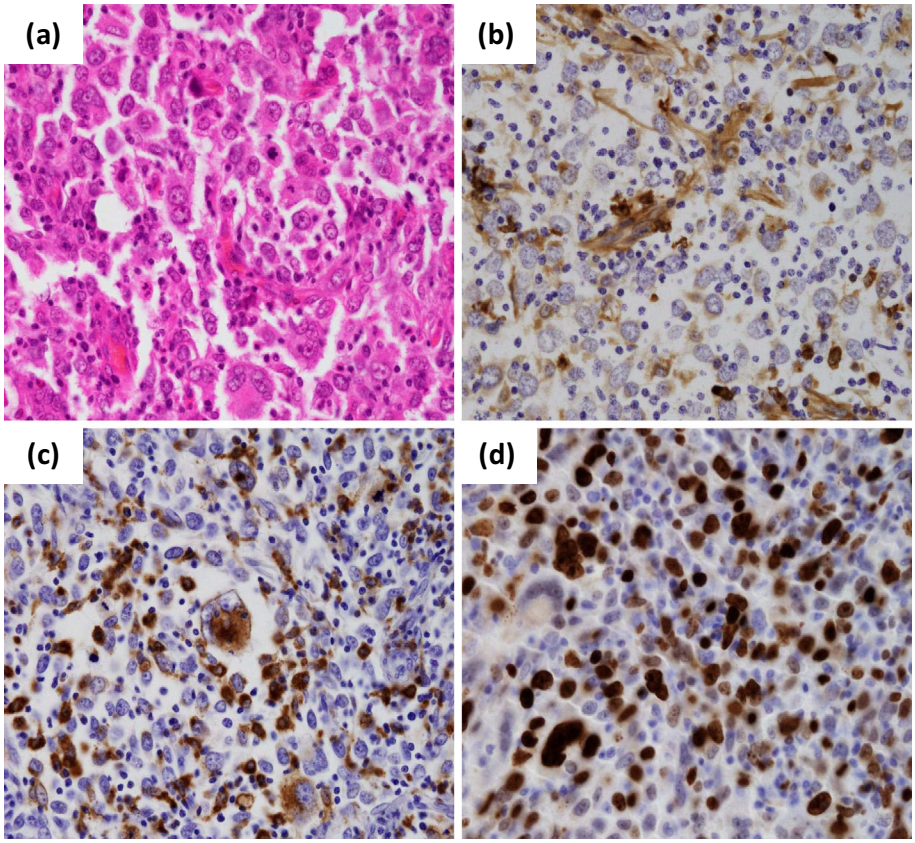

Figure 3. **(a) Mass B showed diffuse infiltration of large and irregular pleomorphic cells with lobulated nuclei and some binucleated and trinucleated cells containing abundant blue cytoplasm (Hematoxylin and Eosin staining, ×400). (b) Neoplastic cells were positive for lysozyme (×400). (c) Neoplastic cells were positive for CD68 (×400). (d) Neoplastic cells were also positive for CD163 (×400).**

paraffin-embedded tumor tissue and the mutation statuses of the RAS (exon 2, 3, 4) and BRAF (exon 15V600) genes were assessed using a polymerase chain reaction enzyme-linked mini-sequence assay-based DNA sequencing method (SRL, Tokyo, Japan). These mutations were not detected in the patient. After resection of the tumor and lymph nodes, a whole-body CT scan showed no abnormalities, but serum sIL2R level was 620 U/mL. Thus the patient received cyclophosphamide (750 mg/m^2, day 2), doxorubicin (50 mg/m^2, day 2), vincristine (1.4 mg/m^2, day 2) and prednisolone (50 mg/m^2, days 2 to 6) (CHOP) chemotherapy. After 4 courses, the patient's serum sIL2R level was 203 U/mL and complete remission of HS was confirmed on PET/CT (Fig. 1b). The condition of the patient has since remained stable for four years with no relapse.

Discussion

HS is an extremely rare non-Langerhans cell disorder with an aggressive course and limited treatment options. It has a distinctive tumor biology, variable clinical presentation, and no standardized treatment. Despite the low incidence of HS, there have been a number of cases of HS reported as secondary events after hematological malignancies (5-10). Limited immunophenotypic/genomic data and overlap with the histopathological characteristics of various other forms of non-Hodgkin lymphomas have previously led to controversy surrounding the diagnosis of HS. Three major putative mechanisms have been proposed for the molecular transformation of B-cell lymphoma to HS: (i) direct transdifferentiation; (ii) a two-step process of transformation with initial dedifferentiation of neoplastic B cells to early progenitors and subsequent redifferentiation; and (iii) possible origin from a common neoplastic progenitor with differentiation along both B-cell and histiocytic/dendritic lineages at different times (2). Mutations involving the RAS-MAPK signaling pathway, BRAF V600E mutations, as activation of PI3K and the tumor suppressor gene CDKN2A have been most frequently reported (11). In this case, RAS and BRAF V600E mutations were not detected, and the origins of the two tumors were distant. A clonal relationship, such as is observed in hematological malignancies, was considered unlikely.

Broadwater et al. reported that the survival of patients with secondary HS was very poor, with a mean survival time of 11.8 months (12). In their report, all 6 patients with secondary HS (2 patients had history of hematological malignancy and 4 patients had a history of solid tumor) received chemotherapy or radiotherapy; thus, therapy-related HS is a possibility. In contrast, the present case did not have

any history of chemotherapy or radiotherapy.

To our knowledge, this is the first reported case involving the concurrent occurrence of HS and any type of carcinoma. There might be another unknown relationship between HS and squamous cell carcinoma. A previous report showed histiocytosis and non-specific lymphocyte predominance in tumors removed from patients with squamous cell carcinoma (13). This case showed that HS and squamous cell carcinoma were located in an adjacent region (Fig. 2a, b). Regarding the possibility of another unknown relationship, the occurrence of this rare HS case might be related to the alteration of the surrounding immune cell populations along with invasion by squamous cell carcinoma.

HS is an invasive tumor that responds poorly to treatment and for which there is no widely-accepted or effective therapy. Since the vast majority of patients are at an advanced stage when they seek medical advice, the survival time is usually less than 2 years due to a poor response to chemotherapy. Nonetheless, some patients may respond to chemotherapy with/without radiotherapy and have a relatively indolent clinical course. In general, efficacy depends on a variety of factors, the most important being the location and stage of tumor (e.g., central nervous system and disseminated lesions). The size of the tumor is also an important factor affecting the prognosis and survival time of patients with a primary tumor diameter of >3.5 cm (4). In the present case, the early stage and relatively small tumor size may have been associated with the favorable outcome.

There is no standard protocol for the management of HS due to the rarity of this disease. HS patients usually present with disseminated disease; thus, they often have a poor prognosis. The most frequent therapy for advanced disease is the CHOP regimen, which is not associated with long-lasting remission. CHOP-E, BEAM and MEAM have been performed in the past. Novel approaches using treatments such as thalidomide (14), alemtuzumab (15) and vemurafenib (16), have also been attempted in a few cases, with good therapeutic responses. Allogenic-stem cell transplantation is mainly performed for relapsed HS and a few cases with a complete response have been documented (17). Further study on patients ineligible for stem cell transplantation patients, such as our case, is necessary.

This is the first case of incidental HS concomitant with laryngeal carcinoma. HS is a rare disease; however, clinical suspicion with well-planned diagnostic procedures is helpful for making a prompt diagnosis. The diagnosis of HS mainly relies on the morphology and immunohistochemistry. A correct diagnosis may lead to timely treatment and improved OS.

The authors state that they have no Conflict of Interest (COI).

References

1. Takahashi E, Nakamura S. Histiocytic sarcoma: an updated literature review based on the 2008 WHO classification. J Clin Exp Hematop **53**: 1-8, 2013.
2. Ansari J, Naqash AR, Munker R, et al. Histiocytic sarcoma as a secondary malignancy: pathobiology, diagnosis, and treatment. Eur J Haematol **97**: 9-16, 2016.
3. Pileri SA, Grogan TM, Harris NL, et al. Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology **41**: 1-29, 2002.
4. Hornick JL, Jaffe ES, Fletcher CDM. Extranodal histiocytic sarcoma: clinicopathologic analysis of 14 cases of a rare epithelioid malignancy. Am J Surg Pathol **28**: 1133-1144, 2004.
5. Cattoretti G, Villa A, Vezzoni P, Giardini R, Lombardi L, Rilke F. Malignant histiocytosis. A phenotypic and genotypic investigation. Am J Pathol **136**: 1009-1019, 1990.
6. Brunner P, Rufle A, Dirnhofer S, et al. Folliular lymphoma transformation into histiocytic sarcoma: indications for a common neoplastic progenitor. Leukemia **28**: 1937-1940, 2014.
7. Michonneau D, Kaltenbach S, Derrieux C, et al. BRAF(V600E) mutation in a histiocytic sarcoma arising from hairy cell leukemia. J Clin Oncol **32**: e117-e121, 2014.
8. Isaacson PG, O'Connor NT, Spencer J, et al. Malignant histiocytosis of the intestine: a T-cell lymphoma. Lancet **2**: 688-691, 1985.
9. Kamel OW, Gocke CD, Kell DL, Cleary ML, Warnke RA. True histiocytic lymphoma: a study of 12 cases based on current definition. Leuk Lymphoma **18**: 81-86, 1995.
10. Lauritzen AF, Delsol G, Hansen NE, et al. Histiocytic sarcomas and monoblastic leukemias. A clinical, histologic, and immunophenotypical study. Am J Clin Pathol **102**: 45-54, 1994.
11. Shanmugam V, Griffin GK, Jacobsen ED, Fletcher CDM, Sholl LM, Hornick JL. Identification of diverse activating mutations of the RAS-MAPK pathway in histiocytic sarcoma. Mod Pathol **32**: 830-843, 2019.
12. Broadwater DR, Conant JL, Czuchlewski DR, et al. Clinicopathologic features and clinical outcome differences in de novo versus secondary histiocytic sarcomas: a multi-institutional experience and review of the literature. Clin Lymphoma Myeloma Leuk **18**: e 427-e435, 2018.
13. Gallo O, Libonati GA, Gallina E, et al. Langerhans cells related to prognosis in patients with laryngeal carcinoma. Arch Otolaryngol Head Neck Surg **117**: 1007-1010, 1991.
14. Abidi MH, Tove I, Ibrahim RB, Maria D, Peres E. Thalidomide for the treatment of histiocytic sarcoma after hematopoietic stem cell transplant. Am J Hematol **82**: 932-933, 2007.
15. Shukla N, Kobos R, Renaud T, et al. Successful treatment of refractory metastatic histiocytic sarcoma with alemtuzumab. Cancer **118**: 3719-3724, 2012.
16. Idbaih A, Mokhtari K, Emile JF, et al. Dramatic response of a BRAF V600E-mutated primary CNS histiocytic sarcoma to vemurafenib. Neurology **83**: 1478-1480, 2014.
17. Abu-Sanad A, Warsi A, Michel RP, et al. Long-term remission after autologous stem-cell transplantation for relapsed histiocytic sarcoma. Curr Oncol **19**: e289-e291, 2012.