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— Case report —

A case of cervical esophageal cancer with a supraclavicular abscess

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Key Words：esophageal cancer, supraclavicular abscess, lymph node metastasis

Advanced esophageal cancer is known to cause perforation leading to mediastinitis or mediastinal abscess, however, it is very rare for the cervical abscess to be the initial presentation. Here, we report a case of cervical esophageal cancer which was first diagnosed as a cervical abscess. A 64-year-old female was referred to our hospital with a diagnosis of a cervical abscess in the left supraclavicular fossa. The laryngoscopic result showed no abnormal findings. The abscess was incised and drained under local anesthesia, in addition to wound irrigation and systemic antibiotics, which lead to a quick recovery of her condition. One month after the discharge, a tumor mass increased in her incision, with contrast-enhanced CT showing thickening of the esophagus, which indicated esophageal cancer. Upper gastrointestinal endoscopy revealed advanced cervical and thoracic esophageal cancer (squamous cell carcinoma). Deep cervical abscesses are often caused by dental infection or tonsillitis in the upper neck, but it is rare to form a confined abscess in the supraclavicular fossa. Therefore, malignant tumors should be suspected depending on the location of the cervical abscess.

Introduction

Perforation caused by advanced esophageal cancer is known to cause mediastinitis, but a cervical abscess is rarely the first sign[1)]. Furthermore, abscesses of metastatic lymph nodes have often been reported, but it is very rare to form a confined abscess in the supraclavicular fossa[2)]. Malignant tumors should be suspected depending on the location and nature of the abscess. Here, we report a case of cervical esophageal cancer which was difficult to distinguish from a cervical abscess.

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Case presentation

A 64-year-old Asian female with a three-week history of fever, progressive swelling, and pain in the left side of her neck was referred to our hospital. She had had a lower left molar tooth extracted three weeks ago and has been complaining of pain and swelling in her left neck for two weeks. Her family doctor diagnosed cervical lymphadenitis and administered oral antibiotics, but her symptoms did not improve. The inflammatory response on blood tests was very high, and contrast-enhanced CT scans showed abscess formation in her left supraclavicular fossa. There were no significant findings in the esophagus (Fig. 1). Therefore, the patient was referred to our head and neck

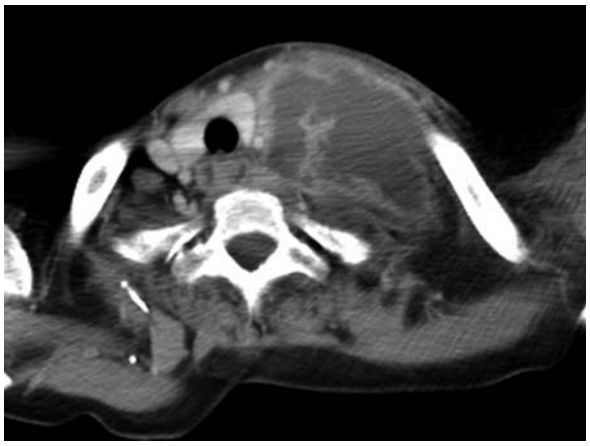

Figure 1

First contrast-enhanced CT showed a poor internal enhanced effect, suggesting abscess formation in the left supraclavicular fossa. There was no tumorous lesion in the esophagus.

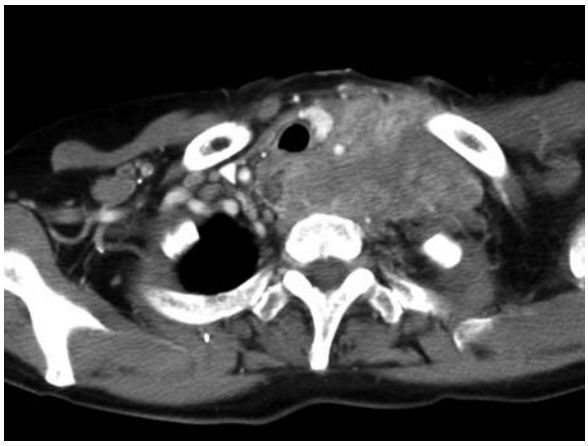

Figure 2

Second contrast-enhanced CT at readmission showed a solid tumor with internal contrast effect, as big as fig.1. The cervical esophageal wall was irregularly thickened and was compressed extramurally by a subclavian tumor, indicating supraclavicular metastasis from cervical esophageal cancer.

surgery department urgently for surgical drainage. She had a 10 years history of depression. She had no smoking and alcoholic history. Physical examination showed no abnormal findings in the oral cavity or pharynx. Laryngoscopy of her throat and chest X-ray also showed normal findings. Admission investigations revealed a leukocytosis of neutrophils with white blood cell counts at 13900 /mcl (reference range 3500-8500 /mcl), high C-reactive protein level at 21.96 mg/dl (reference range 0.00-0.14 mg/dL), normocytic anemia with hemoglobin at 10.1 g/dL (reference range 11.7-14.7 g/dL), low albumin at 3.1 g/dl (reference range 3.4-5.0 g/dL), and normal total protein at 6.9 g/dL (reference range 6.4-8.2 g/dL). T-SPOT.TB test was negative. Soluble interleukin-2 receptor (sIL-2R) was high at 864 U/mL (range 158-623 U/mL). Her abscess was incised and drained under local anesthesia. The culture of the pus from the abscess showed *Streptococcus constellatus*. Surgical drainage and intravenous antibiotics dramatically improved her symptoms and the inflammatory response on blood tests. She was instructed to return to her primary care physician, where she had her wounds cleaned and was given oral penicillin. One month after the discharge, contrast-enhanced CT was performed due to an increased mass in her wound and complaints of dysphagia. The patient was readmitted to our hospital because of a tumorous lesion on the right side of the upper esophagus and an increasing trend of the left neck mass lesion (Fig. 2). The biopsy at the supraclavicular mass showed squamous cell carcinoma. The head and neck area were examined again, including endoscopy, but no primary lesion was found. Upper gastrointestinal endoscopy showed a progressing ulcerative tumor in the cervical and thoracic esophageal mucosa (Fig. 3). Videofluorography showed partial narrowing of the upper esophagus and has shifted to the right side, but there was no fistula formation. Since biopsy from the esophageal ulcer showed squamous cell carcinoma, we concluded that the cervical esophageal cancer resulted in a supraclavicular abscess. After diagnosis, the patient was transferred to another hospital due to difficulty in treatment.

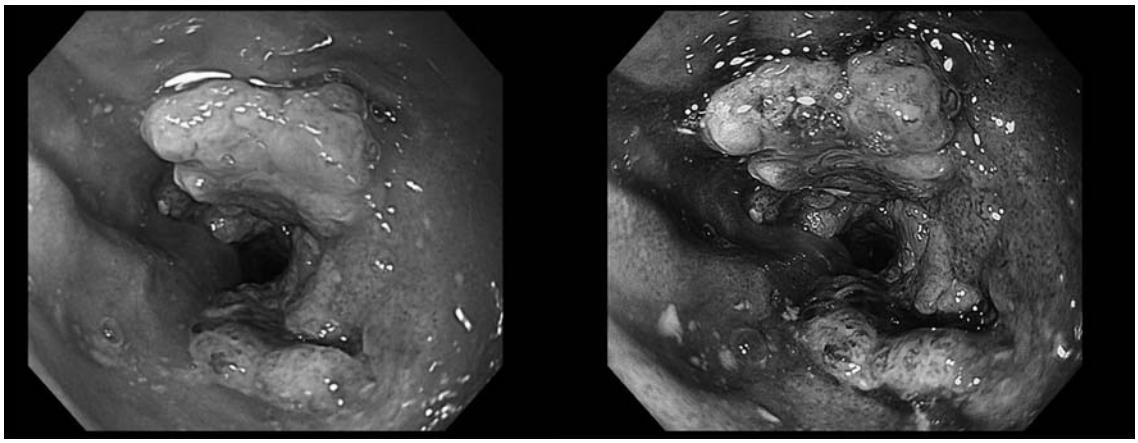

Figure 3

Upper gastrointestinal endoscopy, including narrow-band imaging, showed advanced neoplastic lesions in the cervical esophagus.

The patient was treated with palliative irradiation, but her condition worsened, and she died four months after the initial visit.

Discussion

Dysphagia is the most common initial symptom of esophageal cancer, and pain in swallowing is present in 17% of cases. Other symptoms such as weight loss, dyspnea, cough, hoarseness, and back pain may also be observed[3]. However, detection of a neck infection as the first sign is extremely rare[1]. In this case, esophageal fluorography shows no signs of fistula, suggesting that the metastatic lymph nodes were infected by the hematogenous or lymphatic route and formed an abscess. Although central necrosis is often the cause of abscess formation in metastatic lymph nodes, abscesses are less likely to occur in the head and neck region than in other parts of the body because of the abundant blood flow[2,4]. The fact that the culture from her abscess was *Streptococcus constellatus*, a common oral organism, and the fact that the molar tooth had been extracted by the dentist 3 months before the diagnosis suggests that the disease may have been caused by a dental infection.

Deep cervical infection is a general term for infections occurring in the cervical space, including lymphadenitis, cellulitis, and abscesses. The parapharyngeal space is the most common site of infection, followed by the carotid and posterior pharyngeal space, but cases of abscess formation confined to the supraclavicular fossa have not been reported. Contrast-enhanced CT showed a ring-shaped contrast pattern with an internal low-density region, which indicated not only an abscess but also another benign or malignant lymph node. Benign diseases include histiocytic necrotizing lymphadenitis, tuberculosis, syphilis, and cat-scratch disease, while malignant diseases include metastases from head and neck cancer, distant metastases from organs other than the head and neck, and malignant lymphoma. It is said that metastasis from the primary lesion below the clavicle occurs in the supraclavicular fossa lymph nodes as Virchow's node metastasis, while first metastasis from head and neck cancers occur in others area of the neck[5]. In Japan, supraclavicular lymph node metastasis is classified to be a second or third group of affiliated lymph nodes by upper thoracic and mid-thoracic esophageal cancer or a third group

of metastatic lymph nodes by lower thoracic esophageal cancer[6]. On the other hand, according to the 8th UICC (Union of International Cancer Control) TNM classification, supraclavicular lymph nodes are not included in the regional lymph nodes and are classified as distant metastases (M1). Wen reported[7] that 517 patients (8.7%) with supraclavicular lymph nodes were found in 6,178 patients with thoracic esophageal cancer. The left supraclavicular lymph node, commonly known as the Virchow's lymph node, collects lymph from most of the body, primarily the abdomen. Therefore, lymph node metastasis in the left supraclavicular fossa is considered suggestive of abdominal cancer. On the other hand, the right supraclavicular lymph node receives its supply mainly from the mediastinum, lungs, and esophagus[8]. When recalling these as primary cancer, it is important to pay attention to the bilateral supraclavicular lymph nodes[9]. Metastasis in the supraclavicular lymph node may cause a poor prognosis[5]. Supraclavicular abscesses should be examined with upper gastrointestinal endoscopy.

Conclusions

We report a rare case of thoracic esophageal carcinoma detected by a cervical abscess. A malignant tumor should be suspected behind the abscess when abscess formation is confined to the supraclavicular fossa. Not only head and neck cancers but also metastases from the area below the clavicle should be considered.

Ethical approval

The case report is exempt from ethical approval at our institution.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1) Rehders A, Baseras B, Telan L, et al. Esophageal cancer complicated by esophagopulmonary fistula and lung abscess formation. A surgical approach. Thoracic Cancer 2014；5：468-71.
2) Lee WC, Walsh RM, and Tse A. Squamous cell carcinoma of the pharynx and larynx presenting as a neck abscess or cellulitis. J. Laryngol. Otol 1996；110：893-5
3) Enzinger PC and Mayer RJ. Esophageal Cancer. N Engl J Med 2003；349：2241-52.
4) Thompson HY, Fulmer RP, and Schnadig VJ. Metastatic squamous cell carcinoma of the tonsil presenting as multiple cystic neck masses. Report of a case with fine needle aspiration findings. Acta Cytol 1994；38：605-7
5) Tong C, Luk MY, Chow SM, et al. Cervical nodal metastases from occult primary：Undifferentiated Carcinoma versus squamous cell carcinoma. Head Neck 2002；24：361-9
6) Japan Esophageal Society. Japanese Classification of Esophageal cancer, 11th Edition：Part I. Esophagus. 2017；14：1-36
7) Wen J, Chen D, Zhao T, et al. Should the clinical significance of supraclavicular and celiac lymph node metastasis in thoracic esophageal cancer be reevaluated?. Thoracic Cancer 2019；10：1725-35
8) Mizutani M, Nawata S, Hirai I, et al. Anatomy and histology of Virchow's node. Anat Sci Int 2005；80：193-8.
9) Tanaka T and Ohmichi M, Recurrent ovarian cancer presenting in the right supraclavicular lymph node with isolated metastasis：a case report. Journal of Medical Case Reports 2012；6：176

— Case report —

Bilateral Adrenal Primary Malignant Lymphoma with Inappropriate Secretion of Antidiuretic Hormone

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Key Words：adrenal gland primary malignant lymphoma, bilateral adrenal tumor, syndrome of inappropriate secretion of antidiuretic hormone

Herein, we report a case of bilateral adrenal primary malignant lymphoma with inappropriate secretion of antidiuretic hormone. A 63-year-old man was admitted to Juntendo University Hospital after experiencing weight loss for two months and fever for one month. The blood tests showed normocytic normochromic anemia, liver dysfunction, hypoalbuminemia, hyponatremia, high levels of blood sedimentation, and the presence of sIL-2R. Computed tomography (CT) revealed bilaterally enlarged adrenal glands. We suspected an adrenal primary malignant lymphoma with concomitant inappropriate secretion of antidiuretic hormone. CT-guided bottom adrenal gland biopsy was performed. Beause the histopathology showed a diagnosis of diffuse large B-cell lymphoma (DLBCL), rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP) therapy was administered.

Introduction

Over the past ten years, there has been an increasing number of reports on the incidence of adrenal primary malignant lymphoma；currently, there are approximately 200 reports of cases. The incidence of extra-nodal lymphoma of non-Hodgkin's lymphoma of adrenal origin is less than 1%, with the median survival time being usually within one year, and the prognosis being very poor. Therefore, quick diagnosis and early initiation of chemotherapy is crucial. To the best of our knowledge only one case of bilateral adrenal primary malignant lymphoma complicated with inappropriate antidiuretic hormone secretion (SIADH) has been found, thus we report it in this study, along with a review of literature.

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Case Presentation

A 63-year-old man experienced cold sweats, dyspnea, and numbness in both feet for two months before being hospitalized at the Cranial Nerve Internal Medicine Department of the Juntendo University hospital. Magnetic resonance imaging (MRI) of the head did not reveal any significant findings. Subsequently, he was diagnosed with a transient ischemic attack by a physician, and was treated with clopidogrel and rosuvastatin. However, this was stopped approximately two weeks later because he reported neck pain after initiation of treatment. The patient then consulted our department and was hospitalized for further investigation because he had lost approximately 12 kg over the

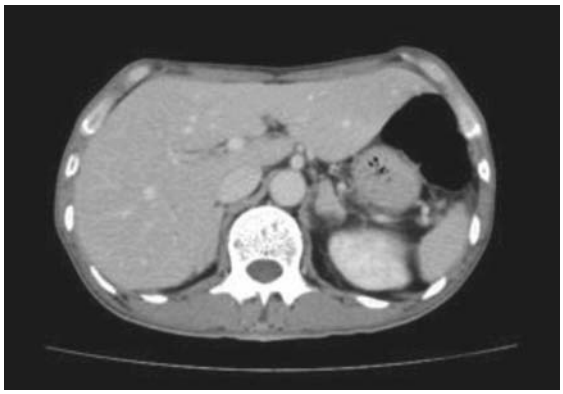

Figure 1 Contrast-enhanced CT of the abdomen

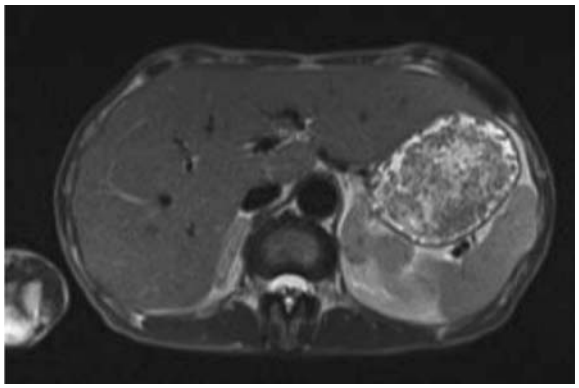

Figure 2 Contrast-enhanced magnetic resonance imaging of the abdomen. (T2WI)

past two months, had a fever of ≥ 38 ℃, and anorexia and night sweats for one month.

A physical examination did not indicate the presence of lymphadenopathy or any other abnormal findings, except for a low BMI. Blood tests showed that he had normocytic normochromic anemia, liver dysfunction, inflammatory reaction hyponatremia, and increased sIL-2R levels. Abdominal ultrasonography showed enlargement of both adrenal glands, with the left adrenal gland measuring 58 × 17 mm and the right adrenal gland measuring 62 × 14 mm. Computed tomography (CT) (Fig. 1) revealed bilateral adrenal enlargement. Moreover, the abdominal cystography MRI (Fig. 2) showed similar bilateral adrenal enlargement with the inside exhibiting a relatively uniform low signal on T1WI and an equal signal on T2WI. The dynamic contrast showed an augmentation effect that was more heterogeneous than that observed in the early phase. There was no lymphadenopathy or ascites.

Because of the patient's symptoms (fever, weight loss, and bilateral adrenal enlargement), we considered differential diagnoses of infections, such as tuberculosis, malignant lymphoma, and adrenal tumor. The blood culture test did not yield any significant bacteria, and the PCR results for tuberculosis and non-

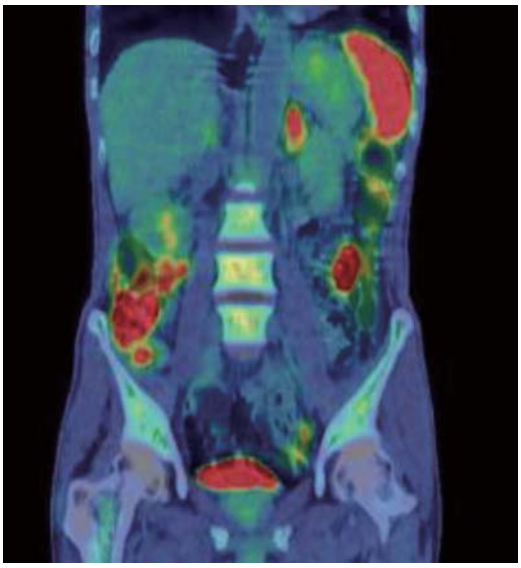

Figure 3 FDG-PET

tuberculous acid-fast bacilli were negative. LDH level was within normal range；however, primary malignant adrenal lymphoma was suspected because enlarged bilateral adrenal lymphoma also presents with similar symptoms (fever, anemia, high ferritin levels, high IL-2R levels) and radiological findings, as seen in this case. Therefore, we performed a PET-CT scan (Fig. 3), which showed bilateral adrenal enlargement in the same area as observed in the contrast CT；in addition, there was strong accumulation of FDG. The spleen showed diffuse enlargement and weak FDG accumulation represented by DLBCL, while the lumbar

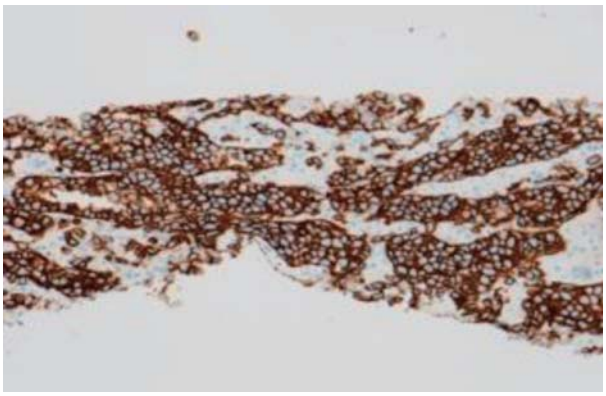

Figure 4 Pathology of adrenal gland
CD20 staining (150x)

vertebrae, femur, and ribs showed light accumulation. We suspected the presence of an intravascular malignant lymphoma and performed a random skin biopsy. We also performed a CT-guided adrenal gland biopsy to diagnose malignant lymphoma and an adrenal tumor. Histopathological examination of the skin revealed mild perivascular lymphocyte infiltration. The adrenal histopathology (Fig. 4) also revealed the presence of a malignant lymphoma with CD3(−), CD5(−), CD10(+), CD20(+), CD79a (+), Bcl-2 (+), Bcl-6(+),

Table 1 Laboratory Data on Admission to Our Department

Hematology		Blood osmolality	272 mOsm/L
WBC	8500 /μL	Ferritin	1602 ng/mL
RBC	347 × 10^4/μL	ADH	0.9 pg/mL
Hb	9.9 g/dL	IL-2R	6910 IU/mL
Ht	30.30%	**Immunity**	
Plt	49.7 × 10^5/μL	IgG	2395 mg/dL
Blood Chemistry		IgG4	76.2 mg/dL
T-bil	0.8 mg/dL	IgA	503 mg/dL
ALP	696 IU/L	IgM	42 mg/dL
AST	90 IU/L	**Endocrine**	
ALT	95 IU/L	TSH	1.31 μIU/mL
LDH	221 IU/L	FT3	1.3 pg/mL
γ GTP	70 IU/L	FT4	1.1 ng/dL
BUN	13 mg/dL	cortisol	19.4 μg/dL
Cre	0.50 mg/dL	ACTH	20.0 pg/mL
UA	2.0 mg/dL	Plasma renin activity	0.8 ng/mL/h
CK	< 5 IU/L	catecholamine	normal
Na	129 mEq/L	**infection**	
K	4.5 mEq/L	EBVAZIgG	(+)
Cl	93 mEq/L	EBVCAIgM	(−)
Ca	7.8 mEq/L	EBNA	(+)
CRP	13.78 mg/dL	EBDRIgG	(−)
Fe	9 μg/dL	T-SPOT	negative
TIBC	99 μg/dL	**Blood Culture**	negative
UIBC	90	**Urinalysis**	
TP	6.6 g/dL	Urinary osmolality	366 mOsm/L
Alb	1.7 g/dL	Urine Na	48 mEq/L
Alb	28.9%	Urine K	22.2 mEq/L
α 1-G	10.1%	Urine metanephrine	0.07 mg/L
α 2-G	13.0%	Urine normetanephrine	0.33 mg/L
β 1-G	5.3%		
β 2-G	9.4%		
γ	33.3%		

MUM-1 (+), and a Ki-67 index > 80%. After the patient was transferred to the hematology department, we received the first report on the pathology of the skin biopsy tissue. The READ system, a diagnostic system for malignant lymphoma in pathology, was used；however, we did not consider intravascular large B-cell lymphoma (IVL). Meanwhile, the second and final reports supported this diagnosis. Based on the above-mentioned results, the patient was diagnosed with diffuse large B-cell lymphoma (DLBCL).

Clinical course

Rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP) therapy was subsequently administered and the patient was discharged without any observed side effects. The patient's sodium level was normal for two months. However, it reduced to 131 mmol/L one month before admission. He was taking clopidogrel and rosuvastatin that was prescribed by a neurologist on an outpatient basis, and he discontinued the treatment 33 days prior to admission. Subsequently, his sodium levels were 129 mmol/L on admission；therefore, he was examined closely. Blood samples and urinalysis revealed normal extracellular fluid. A hormone test was performed as he had hypotonic hyponatremia, but renin and aldosterone levels were also normal, which ruled out mineralocorticoid responsive hyponatremia of the elderly (MRHE). Thyroid function was also normal. There was no cortisol deficiency, normal ACTH, and no pituitary or adrenal hypofunction. Hyponatremia persisted even after discontinuation of oral medications prescribed by the neurologist, and drug-related factors were ruled out. There were no other episodes of polydipsia that could have led to hyponatremia. Based the results of serum osmolality (272 mOsm/L), urine osmolarity (366 mOsm/L), urine Na (48 mmol/L), urine K (22.2 mmol/L), Cre (0.50 mg/dL), cortisol (19.4 μg/dL), and ADH (0.9 pg/mL), the diagnosis of SIADH secondary to lymphoma was made. After admission, fluid intake was restricted from the first day, but the serum sodium level did not increase. Salt supplementation was started 8 days after admission, and 3% saline was administered intravenously 10 days after admission. Nevertheless, the serum sodium concentration did not increase, and the sodium level recovered to normal 50 days after admission to the hospital after the treatment for primary adrenal lymphoma (PAL) was started.

Discussion

The number of cases of malignant primary adrenal lymphoma (PAL) has increased over the past 10 years. At present, 200 cases have been reported[1], with 54% of the cases of PAL being reported in Asia. The average age of diagnosis worldwide is approximately 68 years. The ratio of men to women was found to be 1.8：1 with approximately 70% having bilateral PAL[2,3,4]. The index case was a male of average age, who had bilateral PAL.

PAL has been confirmed in less than 1% of non-Hodgkin's lymphoma cases[5], and has been found to be a diffuse large B-cell lymphoma (DLBCL) in 85-91% of cases[3,6]. Meanwhile, there are fewer cases of adrenal primary IVL reported. The index case was diagnosed as IVL. Although the etiology of PAL has not yet been identified, autoimmune-related infections and immunodeficiencies that are due to polymeric associations cause the appearance of hematopoietic tissue in the adrenal gland in a bid to stop mutations of EBV infection；in addition, the p53 and c-kit genes have been found to be

etiological factors[6,8,9]. However, the index case showed only the presence of an existing EBV infection. According to the results of the plasma and urinary osmotic pressure, electrolyte, and plasma vasopressin level, this was a case of hypo-osmotic hyponatremia merged with SIADH that was associated with a malignant lymphoma. There has been one previous report of a case of IVL and SIADH. It has been proposed that the malignant lymphoma produces IL-6 and IL-1 β, and cytokines which stimulate the hypothalamus to produce vasopressin[7]. The SIADH that developed in this case may have occurred through a similar mechanism.

The clinical manifestation of PAL includes symptoms such as stomach ache, anemia, weight loss, fever of unknown origin, hypercalcemia, thrombocytopenia, and adrenal insufficiency. The patient presented with fever, weight loss, night sweats, anemia, and thrombocytopenia. The differential diagnoses were bilateral adrenal masses and metastatic diseases (lung cancer, lymphoma, melanoma, renal carcinoma, and ovarian cancer), adrenocortical carcinomas, pheochromocytomas, myelolipomas, nodular adrenal hyperplasias, congenital adrenal hyperplasias, functional adenomas, invasive causes (sarcoidosis), and infections (tuberculosis, cryptococcosis, and histoplasmosis).

The symptoms displayed in this case were atypical：fever, weight loss, night sweats, cytopenia (anemia and thrombocytopenia), and high IL-2R levels；therefore, malignant lymphoma was highly suspected. Furthermore, we performed an abdominal ultrasonography and systemic CT, the results of which did not show a clear lymphadenopathy. The results indicated only adrenal enlargement, leading to the suspicion of PAL. In addition, age, bilateral lesions, adrenal insufficiency, serum LDH, and the performance status (PS) of the patients were found to influence prognosis[10,11].

The treatment of IVL is chemotherapy with R-CHOP therapy (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone), with a better prognosis after the administration of this treatment. However, as with an adrenal primary malignant lymphoma, the median survival time was approximately one year[12]. Two years have passed since the patient was admitted to the hospital；he is currently experiencing a complete metabolic response (CMR) because of chemotherapy that included six courses of R-CHOP. His PS is now 1 and he continues to make good progress. We will continue to monitor his progress. PAL is a disease with a poor prognosis；rapid diagnosis and early initiation of chemotherapy is necessary. Therefore, it is important to recognize PAL as early as possible；moreover, the discriminant presentation of PAL is critical for early identification.

Conclusions

Bilateral adrenal primary malignant lymphoma has a poor prognosis；therefore, early diagnosis and treatment is necessary. It is important to include this factor in the differential diagnosis. PAL should be considered in cases of adrenal enlargement. Furthermore, if hyponatremia is present, a thorough examination along with a systemic search and a diagnosis of SIADH may provide clues to the cause of the lymphoma.

References

1）Joseph FG, Cook S, Gowda D. Primary adrenal lymphoma with initial presentation concerning for bilateral adrenal pheochromocytomas. BMJ Case Rep 2017；2017：bcr2017220549.
2）Rashidi A, Fisher SI. Primary adrenal lymphoma：a systematic review. Ann Hematol 2013；92：1583-93.

3）Chen P, Jin L, Yang Y, et al. Bilateral primary adrenal diffuse large B cell lymphoma without adrenal insufficiency：a case report and review of the literature. Mol Clin Oncol 2017；7：145-7.
4）Dong A, Cui Y, Wang Y, et al. (18)F-FDG PET/CT of adrenal lesions. AJR Am J Roentgenol 2014；203：245-52.
5）Mozos A, Ye H, Chuang WY, et al. Most primary adrenal lymphomas are diffuse large B-cell lymphomas with non-germinal center B-cell phenotype, BCL6 gene rearrangement and poor prognosis. Mod Pathol 2009；22：1210-7.
6）Grigg AP, Connors JM. Primary adrenal lymphoma. Clin Lymphoma 2003；4：154-60.
7）Morimoto K, Ogihara T, Shiomi T, et al. Intravascular large B-cell lymphoma with preceding syndrome of inappropriate secretion of antidiuretic hormone. Intern Med 2007；46：1569-72.
8）Ohsawa M, Tomita Y, Hashimoto M, et al. Malignant lymphoma of the adrenal gland：its possible correlation with the Epstein-Barr virus. Mod Pathol 1996；9：534-43.
9）Padhi S, Sahoo J. Primary adrenal non Hodgkin lymphoma：changing trends. Turk J Gastroenterol 2015；26：85-6.
10）Meyyur Aravamudan V, Kee Fong P, Sam YS, et al. A rare case of primary bilateral adrenal lymphoma. Case Rep Med 2017；2017：1251950.
11）Khurana A, Kaur P, Chauhan AK, et al. Primary non-Hodgkin's lymphoma of left adrenal gland - a rare presentation. J Clin Diagn Res 2015；9：XD01-XD03.
12）Horiguchi K, Hashimoto K, Hashizume M, et al. Primary bilateral adrenal diffuse large B-cell lymphoma demonstrating adrenal failure. Intern Med 2010；49：2241-6.

Conflict of interest The authors declare that they have no conflicts of interest.

— Review article —

Cytokine storm mechanism and treatment in COVID-19

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Key Words：COVID-19, SARS-CoV-2, cytokine storm

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and its associated coronavirus disease 2019 (COVID-19) continues to be a serious public health threat. As of this writing in February 2022, more than 400,000,000 people worldwide have been infected by SARS-CoV-2, and over 6,000,000 have died. SARS-CoV-2 is highly infectious and can lead to multiple-organ failure, mainly triggered by respiratory failure. The most severe cases of COVID-19 often involve a cytokine storm, which is an important factor in multiple-organ failure.

This report gives an overview of the characteristics of SARS-CoV-2, as well as the pathological characteristics and the pathophysiological mechanism of COVID-19 related cytokine storms. The current understanding of COVID-19 treatment is also discussed. Understanding the mechanism of a cytokine storm and the available treatment options is essential to reduce mortality in critically ill COVID-19 patients.

Introduction

The term “cytokine storm” first appeared in a 1992 *Blook* paper titled “Cytokine dysregulation and acute graft-versus-host disease” by JL Ferrara at Mount Sinai Hospital[1,2]. A cytokine storm is a state in which the immune system hyperactivates and causes the body to release too many cytokines into the bloodstream, which becomes life-threatening[2]. As the severity of a case of COVID-19 increases, so does the possibility of a cytokine storm, but it does not occur in all infected patients. In fact, most patients with COVID-19 have no symptoms or recover after only mild symptoms. Risk factors for developing a severe case, and thus a higher chance of a cytokine storm, are age, pre-existing lung, heart or immune system conditions, obesity, and chronic disorders such as diabetes and kidney or liver disease. It is also known that cytokine storm-like symptoms similar to those in COVID-19 are detected as side effects from immunomodulatory drugs[3,4].

Coronaviruses are so named for the ring of crown-like spikes on the envelope of the virus that can look reminiscent of the corona around the sun. There are seven kinds of coronavirus that are known to be contagious to humans. Four of the seven can cause common cold symptoms in the upper airway (nose, throat and pharynx). The other three (SARS-CoV, MERS-CoV, SARS-CoV-2) are β-coronaviruses with positive-strand RNA virus genomes that can infect the lower airway (trachea, bronchi, and lung) and can cause serious to severe symptoms.

In the β-coronaviruses, the corona-like spikes bind to angiotensin-converting enzyme 2 (ACE2), and the infection occurs when the

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virus RNA genome is injected into the ACE2 host cell[4,5]. Infection from any of these three viruses can cause serious inflammation in the lungs. Fatal outcomes have occurred after multiple organ failure. This multiple organ failure is induced by the very cytokines that immune cells produce in order to fight against the virus. Cytokine production becomes uncontrollable, and the overproduced cytokines cause a "cytokine storm," which damages healthy cells[6-10].

However, cytokine storms in Covid-19 patients are rare. Around 80% of those with COVID-19 have only light symptoms, and there are a certain number of people who have no discernable symptoms after being infected and develop antibodies without realizing that they have been infected. As of now, there is no scientifically, medically sound method to predict which patients will eventually have a cytokine storm or even why it is a β-coronavirus that specifically leads to a cytokine storm. However, cytokine storms are said to occur more often in elderly people and those with the pre-existing conditions listed above. Those risk factors indicate the possibility that a robust immune system plays a role in avoiding a cytokine storm from being triggered[9-12].

The details of the molecular mechanism that cause the overactivation of the immune system, as well as the process at the molecular level of how a cytokine storm can be fatal to infected patients, are not yet well elucidated. Also, details such as the molecular mechanism that determines the severity of the symptoms that can lead to organ failure are still unclear. While not every mechanism has been discovered, below is the currently available understanding of the molecular mechanism of the cytokine storm and treatment options.

Cytokine storm mechanism in COVID-19

As SARS-CoV-2 infects the lungs, the innate immune system becomes activated, and the adaptive immune system later responds to the specific virus. If the immune system is working normally at this point, the virus is removed and does not cause serious symptoms[10]. However, in patients that develop a cytokine storm, T-cells, especially T helper cells, become overactivated and produce too much cytokine. The cytokine affects interleukin-6 amplifier (IL-6 amplifier) in non-immune cells, such as aged fibroblasts, especially in alveolar epithelial cells and vascular endothelial cells. Activated IL-6 amplifiers excessively stimulate the NF-κB pathway. The body will then be in a full cytokine storm of IL-6, chemotactic cytokines (chemokines), and other growth factors[3,13]. At the same time, SARS-CoV-2 begins to replicate and assemble new viral particles through ACE2, which eventually causes higher levels of inflammation. The large amount of humoral factor produced from the inflammation triggers T-cell anergy and the virus spreads through vascular endothelial cells into organs other than the lungs[13]. Even more inflammation throughout the body leads to additional humoral factor, and this downward spiral leads to functional failure in organs and can eventually be fatal.

Mechanisms of inflammation amplification by IL-6

Figure1, which shows schematic molecular cascade of the cytokine storm induced by SARS-CoV-2 infection, is modified from Fig. 1 in reference 13. Locally, the activated $CD4^+$ T helper cells produce inflammatory cytokines, chemokines, and amplifying factors that include IL-6. The cytokines produced by the activated cells stimulate both the NF-κB and STAT3

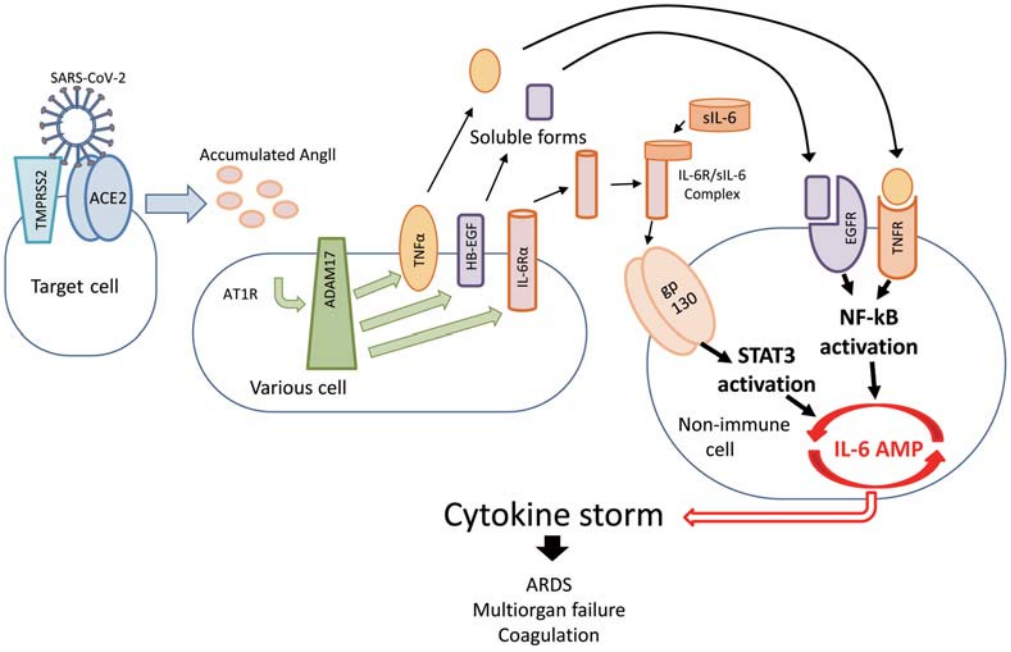

Figure 1 Schematic model of cytokine storm induced by COVID-19 infection through activated IL-6-AMP (modified from a figure in reference 13 ; Hojyo S.et al.).

SARS-CoV-2 infection starts from the binding of the virus to cell membrane-localized ACE2 depending on TMPRSS2 activities. The biding of the virus to ACE2 increases the free Ang II due to a reduction of ACE2-mediated degradation, which activate ADAM17 protease activity via AT1R. ADAM17 and ADAM10 protease cause production of TNF-α, EGF, and sIL-6R α, which activate the IL-6R-STAT3, TNFR- and EGFR-NF-κ B signaling pathways in non-immune cells .Both STAT3 and NF-κ B activation ignite IL-6 AMP, causing cytokine storm, resulting in ARDS, multiorgan failure and fatal intravascular coagulation.

SARS-CoV-2：severe acute respiratory syndrome coronavirus-2 , IL-6：interleukin-6, NF-κ B：nuclear factor-κ B, ACE2：anti-oangiotensin-converting enzyme 2, Ang II：angiotensin II, ARDS：acute respiratory distress syndrome, TMPRSS2：transmembrane protease serine subtype 2

pathways simultaneously in non-immune cells such as fibroblasts or vascular endothelial cells. The IL-6 produced in this process activates STAT3, which in turn continues to activate IL-6 amplifiers. The inflammatory cytokines, amplifying factors, and chemokines produced by the IL-6 amplification mechanisms migrate and the cytokines cause local cells in new areas of the body to activate and proliferate. Moreover, the enhanced IL-6 amplification can contribute to the inflammation becoming chronic, with this continuous induction leading to a cytokine storm, which can occur in both viral and bacterial infections, including in COVID-19, and can lead to the exhaustion and death of the T cells[11,13].

Immune system activation from viral infection

Viral infection induces both an innate and adaptive immune response. An excessive number of inflammatory cytokines that are produced due to an infection in epithelial cells or the innate immune system are called a cytokine storm, while B cells produce antibodies against mainly Hemagglutinin antigen (HA). Moreover, $CD8^+$ T cells produce anti-viral cytokines, which promote virus removal and the recovery of the immune mechanism by killing infected cells recognized by peptides.

Angiotensin II (Ang II) supports homeostasis of the cardiovascular system by upregulating the renin-angiotensin-system and downre-

gulating ACE2. It is reported that angiotensin II signaling through the AT1 receptor pathway promotes inflammation and fibrosis, which can lead to serious acute lung injuries that accompany a cytokine storm, but angiotensin II signaling through the AT2 receptor pathway reduces the effects of inflammation and fibrosis through the Mas receptor[13].

Renin-angiotensin system and lung injuries accompanying cytokine storm caused ARDS and SIRS

Activated AT1 receptor and inhibited AT2 receptor both exacerbate lung injuries that accompany acute respiratory distress syndrome (ARDS). Through the decreased expression of ACE2, the spike proteins in SARS-CoV-2 enhance the Ang II-AT1 pathway, resulting in the exacerbation of lung injuries[13]. Patients meeting the clinical systemic inflammatory response syndrome (SIRS) criteria show inflammation on vascular walls. Immune cells attach to and invade vascular walls, destroying the structures of the wall and causing blood vessel disruption and intravascular stenosis or occlusion occur[10)13)]. Anti-inflammatory steroids can be used to treat SIRS, within limits[8,9,11)].

ACE2, which functions as a receptor of SARS-CoV-2, is expressed in type II pneumocyte myocytes, renal proximal tubule epithelial cells, intestinal or esophageal epithelial cells, as well as in squamous epithelial cells such as nasal and oral mucosa. In order for SARS-CoV-2 to enter a cell, the spike protein needs to be cut off by the transmembrane protease serine 2 (TMPRSS2), which exists on the surface of the cells. In fact, the inhibition of TMPRSS2 inhibited intracellular uptake in experiments. ACE2 antibodies also inhibit the viral intracellular uptake[3,6,13)]. Therefore, molecules that inhibit the bonding of the virus to ACE2 or the inhibition of TMPRSS2 can be expected to effectively suppress viral infection.

Immunotherapy targeting host defense immune mediators

The immune response is triggered by SARS-CoV-2 and can be regulated by targeting mediators that drive various effector mechanisms. These can be non-specific and broad, such as corticosteroids, or specifically targeted inhibitors, such as kinase inhibitors and anti-cytokine drugs[16)].

Corticosteroids

Clinical trials with corticosteroids against COVID-19 have shown their usefulness in a prospective meta-analysis led by the World Health Organization (WHO). These trials provided important evidence for the efficacy of corticosteroids in inpatients with COVID-19 who require assisted ventilation[16)]. The observation that the beneficial effects of corticosteroids are important for critically ill patients might be described by the multifaceted effects of steroids that target a variety of pathophysiological signaling in critically ill patients with COVID-19. It would be important to discuss the appropriate timing of steroid administration in a variety of conditions. Overdosage of corticosteroids, especially in the early stages of the disease, when such treatment can drive adverse effects, remains an important issue[16)].

Kinase inhibitor

Tyrosine kinases have pleotropic effects and are considered attractive targets in the treatment of COVID-19. Tyrosine kinase inhibitors can inhibit cytokine signaling pathways and many immune effector pathways. A double-blind, randomized, placebo-controlled trial of adult patients with COVID-19 and randomly

assigned to receive oral baricitinib (a janus tyrosine kinase (JAK) inhibitor) or placebo for up to 14 days was performed[17]. Patients receiving baricitinib took less time to recover than those in the placebo group (median 7 vs. 8 days). The effect was obvious in the subgroup requiring high flow oxygen or non-invasive ventilation when compared to patients receiving placebo (10 vs. 18 days)[17]. In a Phase Ⅲ, double-blind, randomized, placebo-controlled trial of 1,525 participants, 764 received baricitinib and 76 received placebo. Mortality was reduced by 38.2%, and 28-day all-cause mortality was 8% for baricitinib, and 13% for placebo, with a hazard ratio of 0.57 (95% CI 0.41-0.78)[17]. This was an additional effect on standard of care, including corticosteroids, as 79.3% of participants with available data received systemic corticosteroids at baseline. The FDA recently approved balacitinib for emergency use to treat COVID-19[17].

Target Strategy：Anti-cytokine treatment

Both IL-1 and IL-6 have localized effects such as macrophage activation, endothelial leakage, and extravasation of fluids, as well as systemic effects such as fever, somnolence, and acute phase protein synthesis. Host defense requires the induction of moderate inflammation, but excessive release of these mediators is detrimental[16,17].

Interleukin (IL) -1 receptor antagonist Anakinra is a recombinant human IL-1 receptor antagonist indicated for rheumatoid arthritis (RA) and cryopyrin-associated periodic syndrome. It inhibits the pro-inflammatory cytokines IL-1α and IL-1β. Currently, there are no explicit published controlled clinical trials supporting the efficacy or safety of anakinra in the treatment of COVID-19[17]. In a small sized clinical trial with moderate to severe COVID-19 pneumonia, the use of anakinra was well tolerated and was effective in improving clinical and biological markers. In another cohort study of patients with severe COVID-19, Anakinra reduced both the need for invasive ventilation and mortality in the intensive care unit[17].

Tocilizumab (Actemra®) is a recombinant humanized antibody that can specifically bind to membrane-bound IL-6 receptor (mIL6R) and soluble IL-6 receptor (sIL6R), thereby inhibiting signal transduction. It is a human IL-6 receptor monoclonal antibody[17]. A small scale trial showed its usefulness. The results of future clinical trials will be necessary to clarify its utility[17].

Conclusions

Much useful evidence has been elucidated about the pathophysiological characteristics of COVID-19, the detailed mechanism of cytokine storms, and the construction of therapeutic strategies compared to the early stages of the coronavirus pandemic. Considering the current situation in which new mutant strains of the coronavirus appear repeatedly, there remain a number of issues to be clarified, including the strengthening of global systems for the prevention of pandemics. In this paper, we reviewed the mechanisms of cytokine storms involved in the aggravation of COVID-19 and the current treatment situation.

List of abbreviations

SARS-CoV-2：severe acute respiratory syndrome coronavirus-2
MERS-CoV：Middle East respiratory syndrome coronavirus
ACE2：anti-oangiotensin-converting enzyme 2
IL-6：interleukin-6
NF-κB：nuclear factor-κB
CD4：cluster of differentiation 4

STAT3：signal transducer and activator of transcription 3
HA：hemagglutinin antigen
CD8：cluster of differentiation 8
Ang II：angiotensin II
AT1：angiotensin Ⅱ type 1
AT2：angiotensin Ⅱ type 2
ARDS：acute respiratory distress syndrome
TMPRSS2：transmembrane protease serine subtype 2
IL-6 AMP：interleukin-6 amplifire
ADAM17：disintegrin and metalloproteinase domain-containing protein 7
ADAM10：disintegrin and metalloproteinase domain-containing protein 10
TNF-α：tumor necrosis factor-alpha
EGF：epidermal growth factor
sIL-6Rα：soluble interleukin-6 receptor alpha

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References

1）Antin JH, Ferrara JL. Cytokine dysregulation and acute graft-versus-host disease. Blood 1992；80：2964-8.
2）Ferrara JL, Abhyankar S, Gilliland DG. Cytokine storm of graft-versus-host disease：a critical effector role for interleukin-1. Transplant Proc 1993；25：1216-7.
3）Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med 2020；383：2255-73.
4）Papanikolaou V, Chrysovergis A, Ragos V, et al. From delta to Omicron：S1-RBD/S2 mutation/deletion equilibrium in SARS-CoV-2 defined variants. Gene 2022；814：146134.
5）Kandeel M, Kitade Y, Fayez M, et al. The emerging SARS-CoV-2 papain-like protease：Its relationship with recent coronavirus epidemics. J Med Virol 2021；93：1581–8.
6）Guo W, Porter LM, Crozier TW, et al. Topical TMPRSS2 inhibition prevents SARS-CoV-2 infection in differentiated human airway cultures. Life Sci Alliance 2022；5：e202101116.
7）Krasemann S, Haferkamp U, Pfefferle S, et al. The blood-brain barrier is dysregulated in COVID-19 and serves as a CNS entry route for SARS-CoV-2. Stem Cell Reports 2022；17：307-20.
8）Mehra MR, Desai SS, Kuy S, et al. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med 2020；382：e102.
9）Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020；382：2012-22.
10）Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020；383：120-8.
11）Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020；383：2451-60.
12）Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19)：A Review. JAMA 2020；324：782-93.
13）Hojyo S, Uchida M, Tanaka K, et al. How COVID-19 induces cytokine storm with high mortality. Inflamm Regen 2020；40：37.
14）Atmar RL, Lyke KE, Deming ME, et al. Homologous and Heterologous Covid-19 Booster Vaccinations. N Engl J Med 2022；NEJMoa2116414.
15）Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med 2022. doi：10.1056/NEJMoa2118542.
16）van de Veerdonk FL, Giamarellos-Bourboulis E, Pickkers P, et al. A guide to immunotherapy for COVID-19. Nat Med 2022；28：39-50.
17）Rizk JG, Kalantar-Zadeh K, Mehra MR, et al. Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs 2020；80：1267-92.

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— Review article —

Alcohol-related organ dysfunction in general hospital medicine

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Key Words：Potation, General Medicine

Various factors affect the overall condition of the body, and inappropriate lifestyle habits can lead to a series of abnormalities in various organs that can eventually lead to the development of lifestyle-related diseases. General practitioners need to intervene in inappropriate lifestyles to appropriately treat such diseases. One of the inappropriate lifestyle habits that should be considered is excessive drinking, which has been linked to various health conditions. Previous basic and epidemiological studies have shown that inappropriate drinking habits increase the incidence of five major diseases, with musculoskeletal diseases especially affected：cancer (e.g. colon, esophageal, laryngeal, and breast cancer), neurodegenerative diseases (dementia), diabetes, atherosclerotic diseases (coronary artery disease and stroke), and osteoporosis, the latter of which is the most common cause of a need for nursing care. Social losses due to alcohol consumption are estimated to be four trillion yen per year, and confronting drinking-related conditions has become an urgent issue. During the process of diagnosis, it is important for the primary care physician to thoroughly interview the patient about alcohol use, consider the possible relation of alcohol to the disease, and provide guidance on sobriety and abstinence as needed. Diagnosis, treatment, and lifestyle guidance for alcohol-related disorders by the primary care physician can reduce social losses.

Introduction

In general practice, it is important to focus on the entire body of the patient. Various factors can affect the overall condition of the body, and inappropriate lifestyle habits can lead to a series of abnormalities in various organs, which can eventually develop into lifestyle-related diseases. General practitioners need to intervene in inappropriate lifestyles and treat diseases appropriately[1].

One such inappropriate lifestyle habits that should be considered is inappropriate or excessive drinking[2-3]. The excessive use of alcohol is known to play a major role in diseases such as acute alcohol intoxication, alcoholic hepatitis and cirrhosis, pancreatitis, and Wilnicke's encephalopathy. Recently, alcohol consumption has been found to have a greater impact on the background of various diseases than previously thought.

Previous basic and epidemiological studies have shown that inappropriate drinking habits increase the incidence of five major diseases, with musculoskeletal diseases being the most common：cancer (e.g. colon, esophageal, laryngeal, and breast cancer)[4]；increased resist-

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ance to cancer treatment, such as metastasis[5]；neurodegenerative diseases (e.g. dementia)[6]；diabetes[7]；atherosclerotic diseases (e.g. coronary artery disease and stroke)[8]；and osteoporosis, which is the most common cause of a need for nursing care[9].

Social losses due to alcohol consumption are estimated to be four trillion yen per year, and confronting drinking-related conditions has thus become an urgent issue[10]. In this section, we discuss the relation between alcohol consumption and organ damage, which is important in general practice.

Here, we introduce the recent trends in this field of general medicine.

Alcohol consumption and dementia

Heavy drinking increases the risk of dementia；brain atrophy is more common in alcoholics and heavy drinkers[11], and more people who drink heavily or have abused alcohol develop dementia[6]. Prior studies have identified a positive correlation between the amount of alcohol consumed and the degree of brain atrophy, and brain atrophy caused by alcohol consumption improved with abstinence from alcohol consumption. Conversely, it has been suggested that drinking small amounts of alcohol may help prevent dementia[6]. However, it is important to note that there is no evidence that drinking prevents dementia in people who do not have the habit of drinking.

Alcohol consumption and cancer

During the metabolism of alcohol, ethanol is converted to acetaldehyde by alcohol dehydrogenase (ADH) and metabolized to acetic acid by aldehyde dehydrogenase (ALDH). Alcohol and acetaldehyde are carcinogenic, and individuals with weak functioning of these two enzymes who consume excessive alcohol are at much higher risk of developing oral, pharyngeal, and esophageal cancers. Alcohol consumption has also been shown to cause cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, and breast in women[4]. Ethanol is associated with the metastasis of various cancers[5], and in regards to carcinogenesis related to alcohol consumption, there is no safe amount of alcohol to drink.

Alcohol-related cardiovascular disease

Appropriate drinking is protective against cardiovascular diseases, while excessive drinking is a risk factor. This is from a slightly older study on the cause of coronary artery disease. Daily consumption of two drinks by men and one drink by women can reduce the risk of heart-related death by 20%. Regarding heart failure, drinking about one or two drinks is protective, but drinking more than that increases the incidence of heart failure[12]. Here, “one drink” is equivalent to 12 grams of alcohol. Abstinence from alcohol is essential in cases of alcoholic cardiomyopathy. Small amounts of alcohol can temporarily lower blood pressure；however, long-term habitual drinking can increase blood pressure and cause hypertension.

Regarding arrhythmias, drinking more than four drinks approximately doubles the risk of developing atrial fibrillation[13]. Previous epidemiological studies have shown that appropriate drinking may have a preventive effect against non-hemorrhagic and arrhythmic cardiovascular diseases. The anticoagulant and antioxidant effects of ethanol have been identified as the causes of this phenomenon[8]. In cerebrovascular disease, drinking approximately two drinks is protective against cerebral infarction, but the risk of cerebral hemorrhage increases linearly with increasing alcohol consumption. Recently,

several reports[8] have been published that may negate the J-curve effect of alcohol consumption on cardiovascular disease.

It should be noted that the estimated amounts considered appropriate are averages for the entire study population, and that some individuals may have lower alcohol tolerance depending on their physical constitution and body size. Because some of antiarrhythmic antihypertensive drugs are metabolized by the liver, alcohol consumption should be avoided by patients taking them as it can adversely affect liver function.

Alcohol consumption and diabetes

Although moderate alcohol consumption through proper drinking may prevent the development of diabetes, excessive alcohol consumption can lead to hyperglycemia[7-8]. Alcohol consumption of approximately 20-25 g per day was reported to reduce the incidence of diabetes in a 2009 report[14], and this effect was confirmed in a 2013 meta-analysis that included 38 observational studies[15]. High alcohol consumption can increase blood sugar levels by affecting the fat stored in the liver and suppressing insulin secretion by the pancreas. High alcohol consumption is the largest and most important cause of elevated blood glucose levels owing to excessive energy intake during drinking and meals. Long-term excessive alcohol intake leads to alcoholic cirrhosis and pancreatitis[16]. Alcoholic cirrhosis leads to hyperglycemia, and alcoholic pancreatitis leads to both hyperglycemia and hypoglycemia due to the destruction of alpha and beta cells in the pancreas.

Drinking and dyslipidemia

Because correlations between plasma lipids and alcohol intake are related to sex, age, bodymass index, and ApoE genotype[17], an adequate consumption volume of ethanol cannot be unconditionally defined[8]. The risk of cardiovascular diseases in heavy drinkers seems to be enhanced in patients with the apolipoprotein E4 allele, interleukin-6-174 polymorphism, and cholesteryl ester transfer protein TaqIB polymorphism. Single nucleotide polymorphisms may influence the relation between alcohol consumption, high-density lipoprotein (HDL) cholesterol level, and atherosclerotic risk. Ethanol is unique among toxin, in that it perturbs almost all aspects of hepatic lipid metabolism. Various mechanisms have been suggested to affect mitochondrial β-oxidation, fatty acid, and triglyceride synthesis[18]. A meta-analysis of patients with nonalcoholic fatty liver disease (NAFLD) showed that triglyceride and HDL levels were not significantly different between alcohol drinkers and non-drinkers[19]. In contrast, other than NAFLD patients, it is widely accepted that alcohol consumption increases the HDL cholesterol level in a dose-dependent manner. The effects on LDL and triglycerides have been well elucidated[20].

Discussion

As aforementioned, habitual alcohol consumption can cause a variety of damage to systemic organs. Social losses due to alcohol consumption are estimated to be four trillion yen per year, and confronting drinking-related conditions has become an urgent issue[10]. The economic cost of excessive alcohol consumption in the United State was 223.5 billion dollars (approximately 26 trillion yen) in 2006.

Problems associated with inappropriate alcohol consumption are thus a pressing issue that must be resolved[21]. When diagnosing a patient's condition, it is important for the primary care physician to thoroughly interview the patient about alcohol use, consider the possible relation of alcohol to the disease, and provide guidance on sobriety and abstinence as needed. Patient awareness of alcohol-related diseases is extremely important. In this regard, the website of the Ministry of Health, Labour and Welfare is also useful, although the data used are somewhat outdated[22]

With this in mind, general physicians should pay serious attention to alcohol consumption and manage patients' drinking habits to achieve a healthy society and promote longevity.

References

1）Japanese society of hospital general medicine：Hospital general medicine, Daidougakkan, Fukuoka, Japan 2017.
2）GBD 2016 Alcohol Collaborators：Alcohol use and burden for 195 countries and territories, 1990-2016：a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018；392：1015-35.
3）World Health Organization：Alcohol. https://www.who.int/news-room/fact-sheets/detail/alcohol. Viewed on May 1, 2022.
4）Rumgay H, Murphy N, Ferrari P, et al.：Alcohol and cancer. Nutrients. 2021；13：3173.
5）Rodriguez F, Coveñas R：Biochemical mechanisms associating alcohol use disorders with cancers. Cancers (Basel). 2021；13：3548.
6）Ballard C, Lang I：Alcohol and dementia：a complex relationship with potential for dementia prevention. Lancet Public Health. 2018；3：e103-e104.
7）Knott C, Bell S, Britton A：Alcohol consumption and the risk of type 2 diabetes. Diabetes Care. 2015；38：1804-12.
8）Minzer A, Losno R, Casas R：The effect of alcohol on cardiovascular risk factors. Nutrients. 2020；12：912.
9）Pasco J, Anderson K, Hyde N, et al.：High alcohol intake in older men and the probability of osteoporotic fracture according to the FRAX Algorithm. Nutrients. 2021；13：2955.
10）Ozaki Y：Epidemiology of Alcohol (in Japanese). Journal of Clinical and Experimental Medicine. 2015；254：896-900.
11）Evangelou E, Suzuki H, Bai W, et al.：Alcohol consumption in the general population is associated with structural changes in multiple organ systems. Elife. 2021；10：e65325.
12）Thun M, Peto R, Lopez A, et al.：Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med. 1997；337：1705-14.
13）Csengeri D, Sprünker N, Castelnuovo A, et al：Alcohol consumption, cardiac biomarkers, and risk of atrial fibrillation and adverse outcomes. Eur Heart J. 2021；42：1170-7.
14）Baliunas D, Taylor B, Irving H, et al.：Alcohol as a risk factor for type 2 diabetes：A systematic review and meta-analysis. Diabetes Care. 2009；32：2123-32.
15）Knott C, Bell S, Britton A：Alcohol consumption and the risk of type 2 diabetes：a systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. Diabetes Care. 2015；38：1804-12.
16）Schwarzinger M, Thiébaut S, Baillot S, et al.：Alcohol use disorders and associated chronic disease - a national retrospective cohort study from France. BMC Public Health. 2017；18：43.
17）Ceci F, Ceccanti M, Petrella C, et al.：Alcohol drinking, apolipoprotein polymorphisms and the risk of cardiovascular diseases. Curr Neurovasc Res. 2021；18：150-61.
18）You M, Arteel G：Effect of ethanol on lipid metabolism. J Hepatol. 2019；70：237-48.
19）Kwon I, Jun D, Moon J：Effects of moderate alcohol drinking in patients with nonalcoholic fatty liver disease. Gut Liver. 2019；13：308-14.
20）Chiva-Blanch G, Badimon L：Benefits and risks of moderate alcohol consumption on cardiovascular disease：Current findings and controversies. Nutrients. 2019；12：108.
21）Bouchery E, Harwood H, Sacks J, et al.：Economic costs of excessive alcohol consumption in the U.S., 2006. Am J Prev Med. 2011；41：516-24.
22）Ministry of Health, Labour and Welfare Japan：e-healthnet -Alcohol-. https://www.e-healthnet.mhlw.go.jp/information/alcohol. 2022；Viewed on May 1.

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— Key Image of General Medicine —

Characteristic Findings of Omicron Throat

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Key Words：omicron, SARS-CoV-2, COVID-19

The coronavirus infection (COVID-19) continues to be epidemic with repeated mutations. The mutant strain B.1.1.529 (Omicron strain), which was reported to have first occured in South Africa in November 2021, is more infectious in the upper airway than the mutant strains previously reported, indicating that Omicron may cause severe inflammation in the upper respiratory tract[1)].

We present a case of COVID-19 with characteristic throat findings. A 26-years-old Asian male presented to the emergency department with a 1-day history of high fever and severe sore throat. A nasopharyngeal polymerase chain reaction test was positive for SARS-CoV-2. He complained of a very strong sore throat, leading to difficulty in speaking and swallowing saliva. An otolaryngologist was called to evaluate the upper respiratory tract. Disposable video rhinolaryngoscopy showed white exudate concentrated on the posterior palatal arch (Fig. 1) and laryngeal vestibule mucosa (Fig. 2), which are indicated to be characteristic of throat findings in omicron pharyngitis/laryngitis[2)]. Sotrovimab and intravenous dexamethasone were given to prevent upper airway obstruction.

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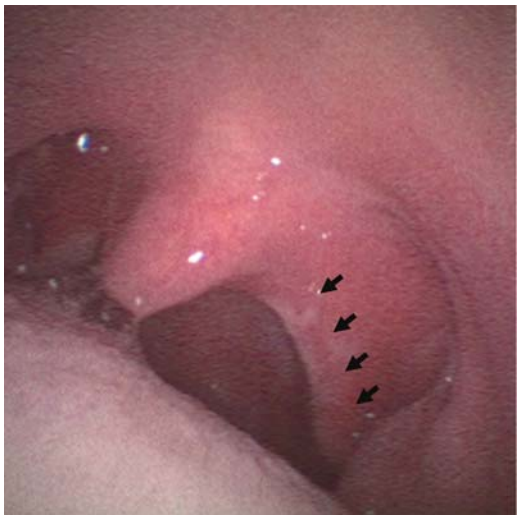

Figure 1 Transoral fiber-endoscopic finding

The soft palate is edematous and reddish with white exudate on the edge of the posterior palatal arch.

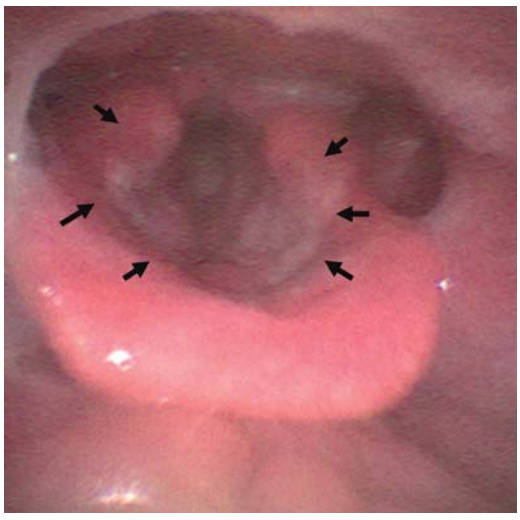

Figure 2 Transnasal fiber-endoscopic finding

White exudate is localized to the vestibule of the larynx.

Before the Omicron pandemic, localized white exudate in the laryngeal vestibule was usually regarded as being from viral croup due to RS viruses or parainfluenza viruses. Currently, it is important to consider that this finding may indicate an omicron infection.

The larynx is composed of the laryngeal vestibule, the tongue side of the epiglottis, the vocal fold, and the arytenoids. Histologically, the laryngeal vestibule is mainly covered with pseudostratified ciliated epithelium, in contrast to the others that are covered with squamous epithelium. Oropharynx mucosa is dominated by the ciliated epithelium on the nasal side and the squamous epithelium on the pharyngeal side. The posterior palatal arch mucosa is presumed to have a high proportion of ciliated epithelium because it is located at the boundary between the nasal and the oral cavities.

These characteristic endoscopic findings, white exudate localized in the posterior palatine arch and laryngeal vestibule, may be observed probably because Omicron is as prone to inflammation on the ciliated epithelium, as are the reported characteristics of SARS-CoV-2[3)].

Upper airway obstruction should be suspected if there is inspiratory wheezing, muffled voice, severe pain, or dysphasia, even without oxygen desaturation. Upper airway stenosis does not reduce oxygen saturation until just before the patient suffocates. Note that the patient can be misclassified as mild.

Ethical approval

Case reports are exempt from ethical approval at our institution.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1） UK Heath Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 34 [UK Health Security Agency website]. January 14, 2022. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050236/technical-briefing-34-14-january-2022.pdf. Accessed March 14, 2022

2） K Piersiala, L Kakabas, A Bruckova, et al. Acute odynophagia-a new symptom of COVID-19 during the SARS-CoV-2 Omicron variant wave in Sweden. J Intern Med 2022 Feb 15.

3） J H Ahn, JM Kim, SP Hong, et al. Nasal ciliated cells are primary targets for SARS-CoV-2 replication in the early stage of COVID-19. J Clin Invest 2021；131：e148517.

— Key Image of General Medicine —

Granulomatous Mastitis with Erythema Nodosum and Polyarthritis

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Key Words：granulomatous mastitis, erythema nodosum, polyarthritis

A 32-year-old woman presented to our hospital with fever, arthralgia, and leg pain. Physical examination revealed arthritis in the wrist and knee joints. Erythema with heat, edema, and tenderness was observed on her lower leg, which was diagnosed as erythema nodosum (EN) (Figure 1). A mass with redness and heat was palpated in the outer lower part of her right breast, and an incision scar was observed (Figure 2). The patient had developed right mastitis a month earlier despite breastfeeding over a year ago. She had received antibiotics and drainage at another hospital for a diagnosis of infectious mastitis and breast abscess, but her condition did not improve. Cultures of the drained fluid were negative. Computed tomography showed masses in her right mammary gland, some of which were contrasted in a ring shape, suggesting breast abscess (Figure 3). Vacuum-assisted breast biopsy showed numerous inflammatory cell infiltrates in the mammary tissue and noncaseating granulomas containing epithelioid histiocytes and multinucleated giant cells (Figure 4). There were no pulmonary lesions or lymphadenopathy, and the serum calcium and angiotensin converting enzyme levels were normal. Ophthalmology examination revealed

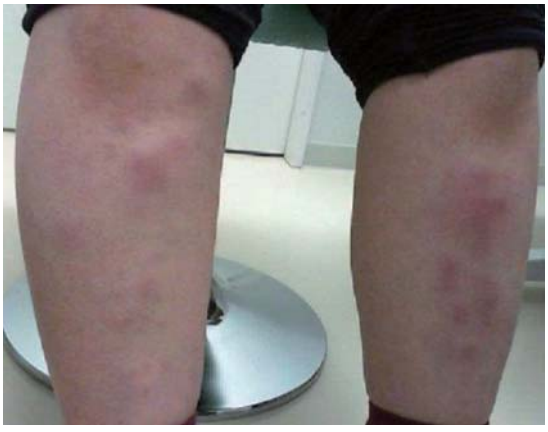

Figure 1

Erythema nodosum on the extensor surfaces of both lower legs

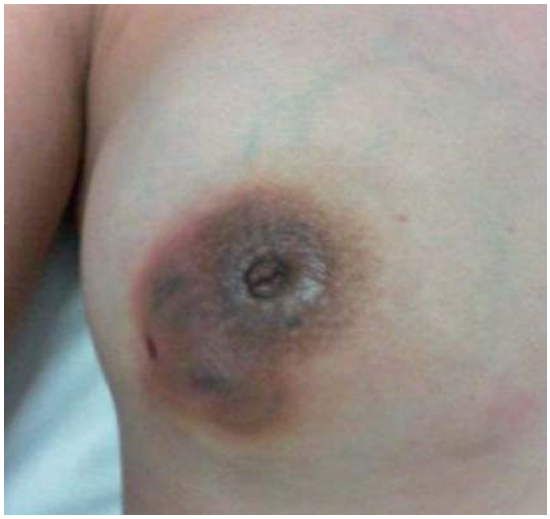

Figure 2

Redness and an incisional scar are observed in the outer lower part of her right breast

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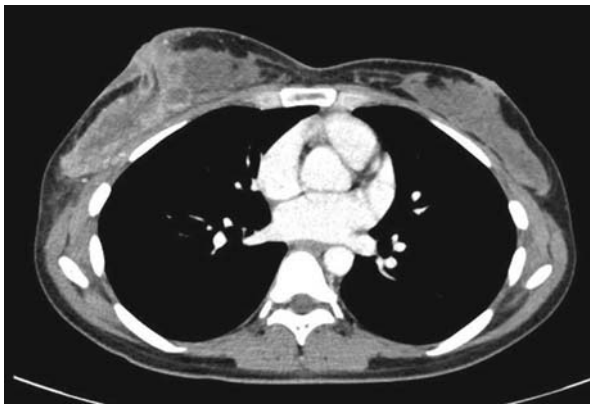

Figure 3

Computed tomography shows masses in the right mammary gland, some of which were contrasted in a ring shape, suggesting breast abscess

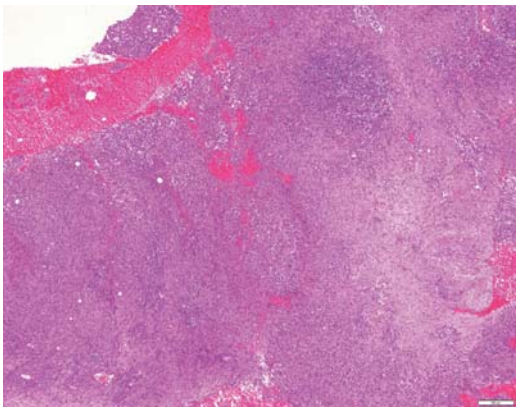

Figure 4

Histopathology shows numerous inflammatory cell infiltrates in the mammary tissue and noncaseating granulomas containing epithelioid histiocytes and multinucleated giant cells

no findings suggestive of sarcoidosis. Sarcoidosis, tuberculosis, breast cancer, autoimmune disease, and streptococcal infection were ruled out based on clinical history and various examinations. Finally, granulomatous mastitis (GM) with EN and polyarthritis was diagnosed.

GM is a rare chronic inflammatory disease of the mammary glands. It is most common among young or middle-aged women with a history of breastfeeding. Infection, prolactin, and autoimmune mechanisms are thought to be involved, but its exact cause remains unknown[1]. GM forms benign masses or abscesses in the breast and is histologically characterized by inflammatory cell infiltrates and noncaseating granulomas. Therefore, the diagnosis of GM is based on the exclusion of cancer and granulomatous diseases, such as sarcoidosis and tuberculosis[1,2]. Furthermore, GM can be complicated by symptoms other than mammary gland symptoms. For example, 18% of GM cases have EN and 14% have arthritis[2]. When mastitis develops during the nonlactating period with EN or arthritis, as in this case, GM should be considered.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1) Altintoprak F, Kivilcim T, Ozkan OV. Aetiology of idiopathic granulomatous mastitis. World J Clin Cases. 2014 ; 2 : 852-8
2) Sarah Ringsted, Marcia Friedman. A rheumatologic approach to granulomatous mastitis : a case series and review of the literature. Int J Rheum Dis. 2021 ; 24 : 526-32

— Key Image of General Medicine —

Milian's ear sign：A woman with a red ear

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Key Words：Milian's ear sign, erysipelas

A 62-year-old woman visited our clinic due to redness of the right ear that began the previous day (Figure 1). Physical examination revealed a slight fever (37.6 ℃), chills, and heat and tenderness on her right ear and preauricular area. There were no blisters on, in, or around the ear. Otoscopy showed no abnormalities of the external auditory canal or tympanic membrane. Blood tests showed an elevated white blood cell count (11,600 cells/μL). Therefore, unilateral ear erysipelas was diagnosed. After oral amoxicillin for 7 days, the redness on the right ear and the preauricular area disappeared.

When redness of the auricle is present, the main differential diagnoses are erysipelas, Ramsay-Hunt syndrome, relapsing polychondritis, and chilblain lupus. In order to differentiate between them, it is necessary to ascertain whether the redness is unilateral or bilateral and whether blisters or tenderness are present. In particular, Ramsay-Hunt syndrome can cause sequelae such as facial paralysis if treatment is delayed；therefore, it is also necessary to check for numbness of the tongue and taste disorders.

If a bacterial infection is suspected as the cause of the auricular redness, erysipelas, which involves infection of the epidermis that extends to the superficial dermis layer, can be diagnosed.

The feature is called Milian's ear sign[1]. Cellulitis, in which the infection is mainly from the deep dermis to the subcutaneous adipose tissue, does not occur because the auricle has a thin dermis and lacks subcutaneous adipose tissue. In this case, acute unilateral auricular redness with tenderness and without blistering, numbness of the tongue, or taste disorder was noted. Therefore, the diagnosis of erysipelas was made.

The pathogenesis of red ears can be inferred by careful anatomical observation. Making the correct diagnosis is important because the treatment and prognosis vary according to the cause.

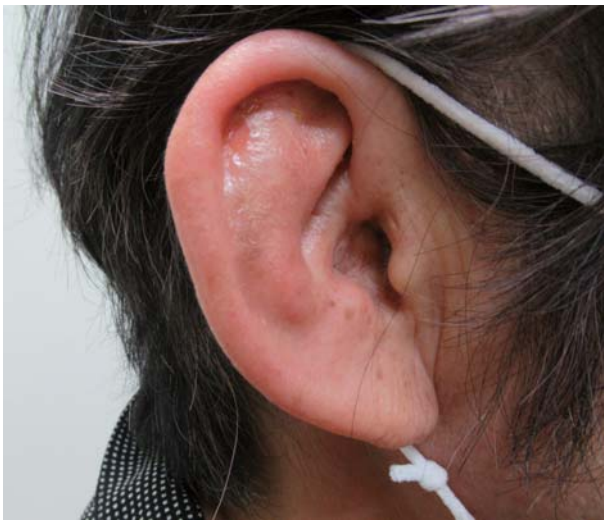

Figure 1

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References

1）Madke B, Nayak C. Eponymous signs in dermatology. Indian Dermatol Online J. 2012；3：159-65.

Conflict of interest The authors declare that they have no conflicts of interest.

— Key Image of General Medicine —

Contrast-enhanced ultrasonographic diagnosis of focal nodular hyperplasia in a 15-year-old boy

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Key Words：focal nodular hyperplasia, contrast-enhanced ultrasonography

A 15-year-old boy with severe intellectual disability was referred for further investigation of a mildly elevated serum gamma-glutamyl transferase level（113 U/L）. He had no other medical history and was not on any medications. Contrast-enhanced computed tomography showed an 11-cm liver tumor with a central stellate scar, which is typical of focal nodular hyperplasia（FNH）（Figure 1）[1]. The liver tumor markers detected were alpha-fetoprotein（2.0 ng/mL, reference range：< 10 ng/mL）and protein induced by vitamin K absence or antagonist-II（30 mAU/mL, reference range：< 40 mAU/mL）. We initially intended to perform gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid（GD-DTPA）-enhanced magnetic resonance imaging（MRI）to differentiate between FNH and fibrolamellar hepatocellular carcinoma；however, we performed contrast-enhanced ultrasonography（CEUS）instead because the patient could not lie still for extended periods of time. CEUS did not detect the spoke-wheel appearance typically observed in FNH, although a small arterial signal in the center of the tumor was detected.（Figure 2）. The tumor was hyperechoic in the arterial

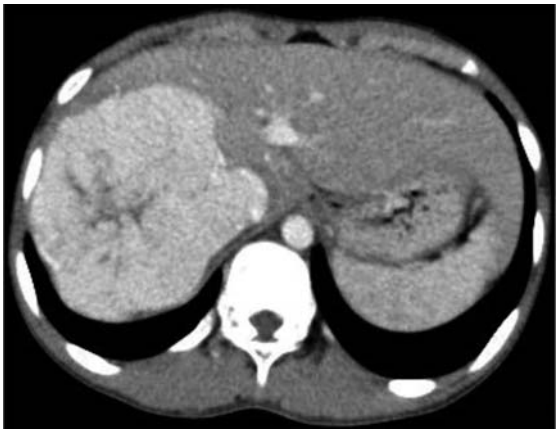

Figure 1 Contrast-enhanced computed tomography of the abdomen

A large tumor is present in the right liver lobe. The tumor displays hyperenhancement in the arterial phase and has a central stellate scar.

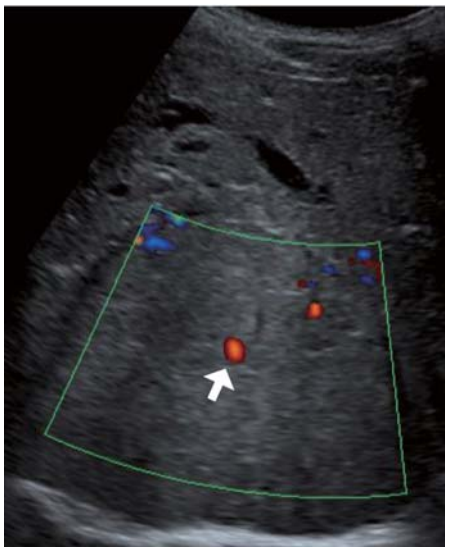

Figure 2 Grayscale ultrasonography of the liver

The liver tumor is homogeneous and isoechoic with the normal liver. The spoke-wheel appearance typically observed in focal nodular hyperplasia is not detected, although there is a small arterial signal in the center of the tumor.

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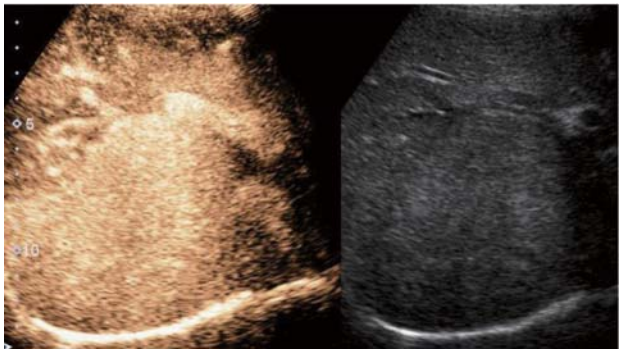

Figure 3 Contrast-enhanced liver ultrasonography in the arterial phase：harmonic and grayscale imaging

The tumor is hyperechoic.

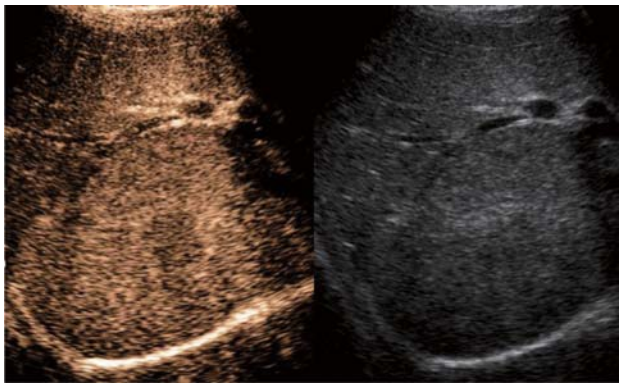

Figure 4 Contrast-enhanced liver ultrasonography in the Kupffer phase：harmonic and grayscale imaging

The tumor is isoechoic.

phase（Figure 3）and isoechoic in the Kupffer phase（Figure 4）. Based on these findings, FNH was diagnosed, and follow-up imaging was performed. The tumor size had not changed at the 2-year follow-up.

FNH is the second most common benign liver tumor after hemangioma[1]. FNH typically develops in women in their 40s and 50s and is rare in adolescent boys[1]. Although the etiology of FNH has not yet been established, it is presumed to be caused by arterial malformations in the liver[1]. The CEUS findings of FNH reflect central vascular blood flow. FNH is hyperenhancing in the arterial phase in ＞ 90% of cases[2]. In the Kupffer phase, the perfusion pattern in FNH is typically hyperechoic or isoechoic, while fibrolamellar hepatocellular carcinoma is hypoenhancing[3]. FNH can be diagnosed with a high probability if the typical enhancement patterns seen on CEUS are detected. CEUS is useful in the diagnosis of FNH when MRI is not available, as in this case.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1）Marrero JA, Ahn J, Rajender Reddy K. American College of Gastroenterology. ACG clinical guideline：the diagnosis and management of focal liver lesions. Am J Gastroenterol 2014；109：1328-47.
2）Piscaglia F, Venturi A, Mancini M, et al. Diagnostic features of real-time contrast-enhanced ultrasound in focal nodular hyperplasia of the liver. Ultraschall Med 2010；31：276-82.
3）Dong Y, Wang WP, Mao F, et al. Imaging features of fibrolamellar hepatocellular carcinoma with contrast-enhanced ultrasound. Ultraschall Med 2021；42：306-13.

— Key Image of General Medicine —

Fibroma caused by years of carrying a portable Shinto shrine：Mikoshi-kobu

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Key Words：hump, lipoma, mass, nuchal-type fibroma, palanquin

Manuscript

A previously healthy 56-year-old man visited our hospital with a complaint of dyspnea on effort. He was diagnosed with an asthma attack because of bilateral expiratory wheeze on auscultation of the lungs and normal cardiac examinations, electrocardiogram, and chest X-ray. He was successfully treated for asthma with a bronchodilator, systemic glucocorticoid, and subsequent corticosteroid inhaler. On examination, we found a soft mass at the nuchal area and right shoulder (Figure 1). The mass was mobile and painless without any rash or pigmentations. The size of the mass was 20 cm x 15 cm. His right shoulder was lower than his left shoulder and the right clavicle was deformed. The patient stated that he had carried Japanese wooden portable Shinto shrines called "mikoshi" for many years in religious festivals, and that he rested the wooden support beam of the portable shrine on his right shoulder. He had noticed that the mass had gradually grown larger over his years of carrying portable shrines. He stated that many of his fellows who carried portable shrines had similar shoulder masses, and they regarded the masses as "badges of honor" for portable shrine carriers.

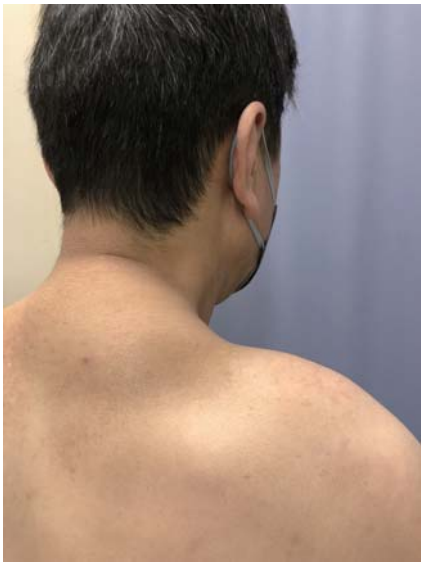

Figure 1

There have been some reports on similar masses, which are known as "mikoshi-kobu" in Japan, from other Asian countries[1-2]. Although the physical findings of the mass resembled those of a lipoma[1], previous reports indicated that these masses were composed of thickened dermal collagenous fibers and interspersed adipose tissue[1-3], which is compatible with a nuchal-type fibroma[2-3]. Because "mikoshi" usually weigh 500-1,000 kg, repetitive and long-term pressure and friction to the shoulder are believed to cause "mikoshi-kobu"[1-2]. As the patient stated that many of his fellows had similar masses, it appears that "mikoshi-kobu" is relatively common in people who carry portable shrines. However, "mikoshi-kobu" is not well

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known to health care providers, probably because patients regard the masses as “badges of honor” and do not seek medical service for them. Given that “mikoshi-kobu” is usually a benign and asymptomatic mass, it is important to ask a patient with such a mass if they are in the habit of carrying heavy loads that cause chronic pressure to the shoulder and nuchal area. Such loads may be portable shrines[1-2] or weights lifted during weight training[3]. This simple clinical query should be performed before considering invasive evaluations such as biopsies when presented with suspicious shoulder masses[1-3].

Conflict of interest The authors declare that they have no conflicts of interest.

References

1） Mitsuhashi K, Hyakusoku H, Fumiiri M. A case of so-called Mikoshi-Kobu. Ann Plas Surg 1990；25：494-6.
2） Lee CC, Lai CS, Lin CH, Lin YN, Chu SC, Chai CY et al. Extra nuchal-type fibroma associated with repetitive blunt trauma during religious activities. Trauma Case Rep 2016；4：16-20.
3） Jayaram PR, Walsh J, Lari H, Mohammad N, Mallinson Pl, Ouellette HA. Repetitive trauma-induced extra-nuchal-type fibroma. Skeletal Radiol 2022；51：681-5.

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