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Lung Cancer Associated with Sweet's Syndrome: Report of a Case

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Abstract
Lung cancer associated with Sweet's syndrome is extremely rare. There are only seven reports of such cases. As far as could be determined from a comprehensive search, there is no reported operative case of lung cancer with this syndrome in the world literature. A 75-year-old Japanese man was diagnosed as having Sweet's syndrome. A chest computed tomography (CT) scan to screen for malignant lesions associated with this syndrome revealed an abnormal shadow in the lung. Although [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography showed no abnormal uptake, lung cancer was most strongly suspected by chest CT. His erythema improved rapidly with steroid therapy and he underwent a segmentectomy (S^6) of the right lower lobe. A pathological examination revealed lung adenocarcinoma (pT1N0M0: Stage Ia). The patient was discharged from the hospital without any worsening of Sweet's syndrome. We herein report a first operative case of an early stage lung adenocarcinoma with this syndrome.

Key words Sweet's syndrome · Malignant pulmonary tumor · Lung cancer · Operation

Introduction

Acute febrile neutrophilic dermatosis (Sweet's syndrome) is characterized by fever, neutrophilia, and painful cutaneous plaques, primarily on the upper extremities, head, and neck. Approximately 10%–15% of cases of Sweet's syndrome occur in patients with cancer.[1] The most common malignancy is hematological, and malignant solid tumors are rare.[1] However, in cases with this syndrome, a search for not only hematological disorders but also for solid tumors should be made. In our case, although [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) showed no abnormal uptake, chest computed tomography (CT) revealed an early stage of lung cancer, and therefore we were able to treat the patient successfully.

Case Report

A 75-year-old Japanese man was referred to our hospital with a complaint of pyrexia and multiple tender erythemas on his face, beginning 2 days earlier (Fig. 1). He had no other symptoms such as arthralgia, myalgia, or recent upper respiratory infection that could cause it to be mistaken for a cold. Gradually, the erythemas increased in size and number, and spread to the extremities. A full blood examination showed a slight leukocytosis of 9200/mm^3, and a neutrophilia of 83.5%. Hemoglobin was 16.0 g/dl. The erythrocyte sedimentation rate was 11 mm/h, and C-reactive protein and serum amyloid A were elevated to 3.9 mg/dl and 164 μg/ml. Histologically, a skin biopsy from a lesion on the right upper extremity demonstrated pustules and prominent edema of the upper dermis, accompanied with dense perivascular inflammatory infiltration. The infiltration was largely composed of neutrophils, accompanied by lymphocytes, eosinophils, histiocytes, and nuclear fragmentation. There was no evidence of vasculitis. These findings were consistent with the features of Sweet's disease (Fig. 2). The patient was admitted to the Department of Dermatology of our hospital and received betamethasone at a dose of 4 mg/day by intravenous injection. All of the skin lesions improved. Oral prednisolone therapy at 30 mg/day was begun and slowly tapered. Chest abdominal CT to screen for malignant

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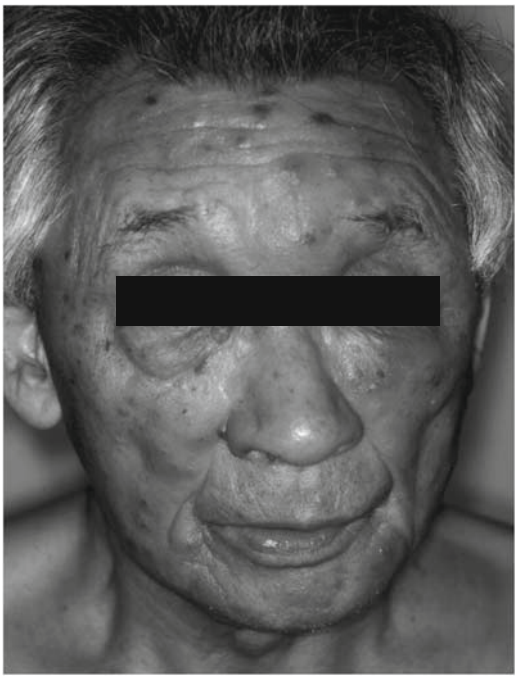

Fig. 1. Multiple tender erythemas on the face

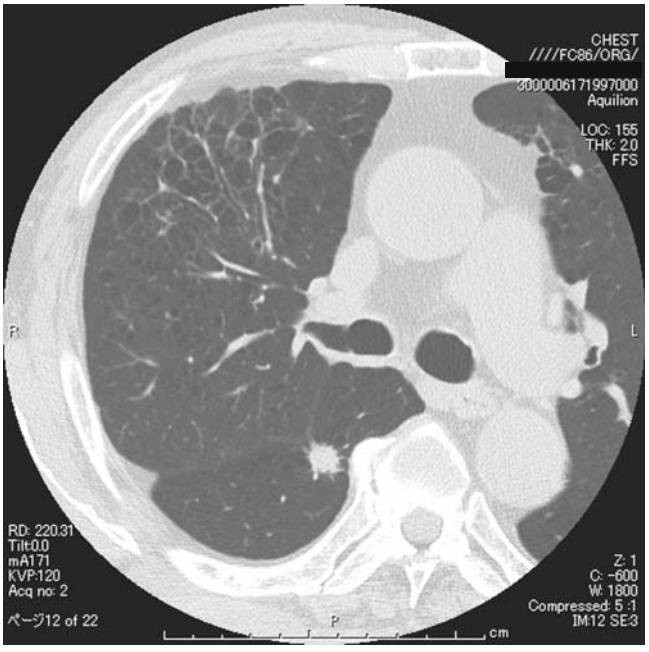

Fig. 3. Chest computed tomography scan showing the shadow of a solid mass with spiculation in the right S^6 region, and emphysematous lung

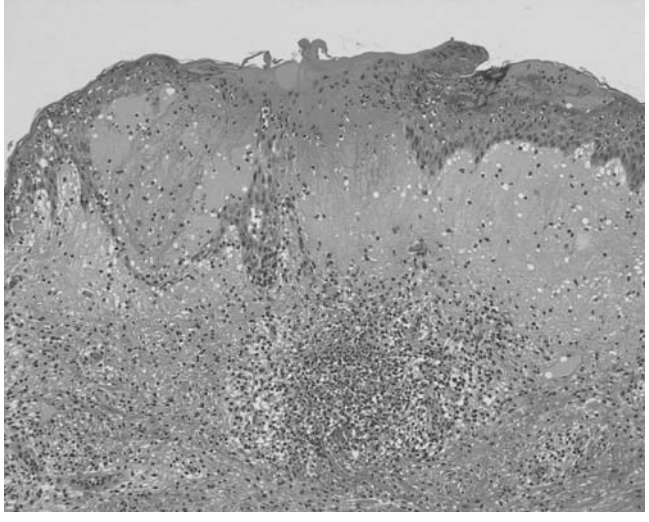

Fig. 2. High-power microscopic view of the skin lesion. The cutaneous infiltration is composed largely of neutrophils, accompanied with lymphocytes, eosinophils, histiocytes, and nuclear fragmentation. These findings are consistent with the features of Sweet's disease (H&E stain, ×25)

lesions associated with this syndrome revealed an abnormal shadow in the right pulmonary lower lobe. A lung tumor with spiculation was located in Segment 6, measuring about 10 mm diameter. There was no lymphadenopathy or pleural effusion. The chest CT also showed bilateral emphysematous lung. Tumor markers (carcinoembryonic antigen, squamous cell carcinoma antigen, sialylated Lewis X-I antigen, and cytokeratin fragment) were within the normal range. No abnormality was seen in the abdomen. Although FDG-PET showed no abnormal uptake (maximum standardized uptake value was 1.4), primary lung cancer was most strongly suspected (Fig. 3). Because the lung tumor was too small, bronchoscopic examination was not performed. The patient was discharged from the hospital and put on prednisolone at 17.5 mg/day orally. One week later, he was readmitted to our ward for the treatment of a lung tumor. He underwent a segmentectomy (S^6) of the right lower lobe and a sampling of lymph nodes by video-assisted thoracoscopic surgery. A frozen diagnosis was lung adenocarcinoma.

His smoking history was 40 cigarettes per day for 30 years and the results of preoperative spirometry of the patient was %VC: 97.4% and $FEV_{1.0\%}$: 76.1%. Because he had suffered from chronic obstructive pulmonary disease (COPD) and had slight dyspnea on effort (Hugh-Jones II°), a lower lobe lobectomy was not performed. The permanent histological diagnosis was the same as the frozen diagnosis. The lung lesion was composed of a proliferation of infiltrating atypical epithelial cells with glandular or papillary structures. Therefore, the diagnosis of adenocarcinoma was made and no metastasis of lymph nodes was seen (pT1N0M0: Stage Ia) (Fig. 4). Although he developed pneumonia on the first postoperative day, his illness was quickly improved

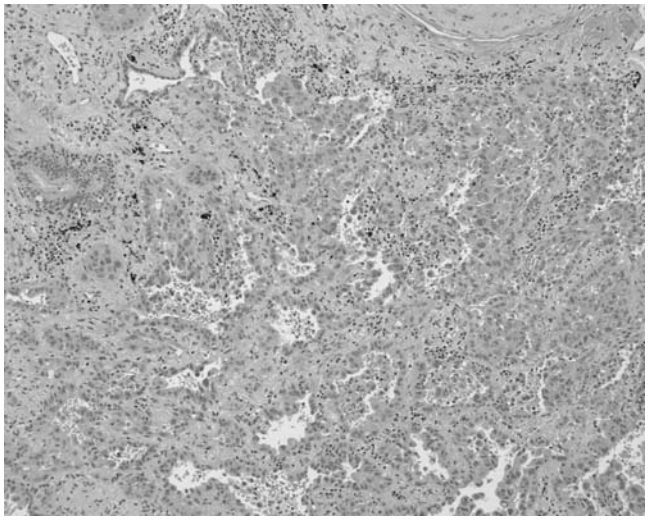

Fig. 4. High-power microscopic view of the lung lesion. The lesion shows proliferation of infiltrating atypical epithelial cells with glandular or papillary structures, consistent with adenocarcinoma (H&E stain, ×25)

by an intravenous dosage of antibiotics. He was discharged from the hospital without any worsening of Sweet's syndrome.

Discussion

Acute febrile neutrophilic dermatosis (Sweet's syndrome) was first described in 1964 by Robert Douglas Sweet.[2] It usually occurs in middle-aged women and the usual age of onset is between 30 and 60 years.[1] Zamanian and Ameri[3] reported the incidence of Sweet's syndrome to be 3 per 10000 among new dermatologic patients and all were women with a mean age of 58 years. Sweet's syndrome is characterized by five cardinal features[1]: (1) pyrexia; (2) neutrophilia; (3) multiple, raised, asymmetric, erythematous, painful cutaneous plaques; (4) a dense dermal infiltrate consisting of mature neutrophils; and (5) a rapid response to steroid therapy. The diagnostic histological finding in Sweet's syndrome by skin biopsy is the presence of a dense dermal infiltrate composed of mature neutrophils.[1] The etiology of this syndrome remains unknown; however, it has been suggested that it may be a manifestation of an abnormal reaction of neutrophilic granulocytes to unknown antigens[4] or might be a hypersensitivity reaction to an infectious or chemical agent, or to tumor-associated antigens.[5] Because of the presence of systemic problems such as arthritis or the response to steroids, several investigators have suggested that an immunologic mechanism is involved.[1] Untreated skin lesions often resolve spontaneously within 3 months.[1,6] More rapid improvement in symptoms and both cutaneous and extra abnormalities can be achieved with steroid treatment.[1]

Sweet's syndrome may occur in an isolated form, but it has often been reported in association with many inflammatory disorders, including ulcerative colitis, Crohn's disease, connective tissue diseases, and respiratory and urinary tract infections.[4] Diverse cutaneous paraneoplastic syndromes, including musculoskeletal disorders (clubbing, hypertrophic osteoarthropathy, dermatomyositis, and multicentric reticulohistiocytosis), reactive erythemas (erythema gyratum persistens and necrotic migratory erythema), vascular dermatoses, papulosquamous disorders (acanthosis nigricans, tripe palms, palmar hyperkeratosis, acquired ichthyosis, pityriasis rotunda, florid cutaneous papillomatosis, and extramammary Paget's disease), and hair growth disorders (hypertrichosis lanuginosa acquisita) may be associated with underlying internal malignancies.[7] Approximately 10%–15% of all published cases of Sweet's syndrome occurred in patients with cancer,[1] so this syndrome is also considered to be paraneoplastic syndrome.[4] The most commonly associated malignancy is hematologic, for example acute myelogenous leukemia.[1] On the other hand, the association with solid tumors is rare.[1] There have been some reports of Sweet's syndrome associated with solid tumors, five cases[1] (up to 1987), eight cases[4] (up to 1993), and 41 cases[6] (up to 1993) in the world literature. In 41 cases with solid tumors, the patients ranged in age from 38 to 78 years (average 59) and 59% were women.[6] Sweet's syndrome preceded either the initial diagnosis of cancer or the detection of asymptomatic metastatic, persistent, or recurrent tumors in 61% of the patients, and in 39% of the patients Sweet's syndrome followed the development of a solid tumor. In addition, the onset of Sweet's syndrome occurred concurrently with or before the discovery of unsuspected metastasis or the detection of a recurrent tumor.[6] The association of solid tumors with Sweet's syndrome was less commonly reported in the literature and it was regarded by some as being merely coincidental. However, Dyall-Smith and Billson[8] reported that the skin eruption appeared to be temporarily related to dissemination in a patient with prostatic adenocarcinoma, and recurred frequently until death.

The most common solid tumors were carcinomas of the genitourinary organs (37%), breast (23%), and gastrointestinal tract (17%).[6] Adenocarcinoma was the most common histological cell type, being observed in 57% cases of solid tumors. Eleven percent of the malignancies were squamous cell carcinoma.[6]

Malignant pulmonary tumor with Sweet's syndrome is very rare, occurring in only 7% of cases.[6] Our PubMed search found only seven cases of malignant pulmonary

Table 1. Characteristics of the patients reported with malignant pulmonary tumors associated with Sweet's syndrome

Case no.	Year	First author[Ref.]	Age (years)	Sex	Histological cell type	Site	Treatment	Preceding lesion	Occasion of tumor discovery	Outcome
1	1988	Dyall-Smith[8]	Unknown	M	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
2[a]	1990	Smolle[9]	56	M	Unknown	Bronchus	Unknown	Unknown	Unknown	Unknown
3[a]	1990	Smolle[9]	62	F	Ad	Unknown	Unknown	Unknown	Unknown	Unknown
4	1993	Nielsen[4]	56	F	Ad	RUL	ChemoTx	Tumor	Unknown	Died
5	1994	Yamamoto[5]	59	M	SCLC	Lt. hilar	RTx	Erythema	Pyrexia	Died
6	2004	Weenig[10]	68	M	Sq	LLL	Unknown	Erythema	Chest CT	Unknown
7[a]	2007	Denhove[11]	56	M	Sq	Bronchus	ChemoTx & RTx	Erythema	Unknown	Surviving
8	Present case		75	M	Ad	RLL	Operation	Erythema	Chest CT for screening	Surviving

Ad, adenocarcinoma; SCLC, small cell lung carcinoma; Sq, squamous cell carcinoma; RUL, right upper lobe; LLL, left lower lobe; RLL, right lower lobe; ChemoTx, chemotherapy; RTx, radiotherapy
[a] English abstract only

tumor associated with this syndrome reported in the English literature. The clinical features of the total of eight cases, including our present case, of malignant pulmonary tumors are summarized in Table 1. They consisted of 6 men (75%) and 2 women (25%). The patients ranged in age from 56 to 75 years. Their mean age was 61.7 years. Histologically, there were 3 cases of adenocarcinoma, 2 of squamous cell carcinoma, 1 of small cell carcinoma, and 2 unknown cases. Malignant pulmonary tumors with this syndrome tended to occur in males, and the age tended to be high in comparison to other solid tumors. There were 5 cases of non-small cell carcinoma (3 of adenocarcinoma and 2 of squamous cell carcinoma) and 1 case of small cell carcinoma. In 4 cases, erythema preceded the lesions. It is unknown why chest CT was performed in case No. 6. We diagnosed an early stage of lung cancer by performing CT to screen for malignant lesions, and the patient was therefore able to undergo an operation for his illness. As far as we know, our case was the only operative case, and therefore this was the first operative case of a malignant pulmonary tumor with Sweet's syndrome.

In patients with newly diagnosed Sweet's syndrome and in whom neither cancer nor any other symptoms have been identified, screening for malignancies should be done. It may be possible to diagnose an unsuspected malignancy at an early stage. Furthermore, after a temporary disappearance or improvement of erythemas by steroid therapy, careful observations for the reappearance of skin lesions and systemic manifestations are necessary, because the onset of Sweet's syndrome suggests the possible development of either a metastatic or a recurrent tumor.

References

1. Cohen PR, Kurzrock R. Sweet's syndrome and malignancy. Am J Med 1987;82:1220–6.
2. Sweet RD. An acute febrile neutrophilic dermatosis. Br J Dermatol 1964;76:349–56.
3. Zamanian A, Ameri A. Acute febrile neutrophilic dermatosis (Sweet's syndrome): a study of 15 cases in Iran. Int J Dermatol 2007;46:571–4.
4. Nielsen I, Donati D, Struma R, Zavarini G, Sartori S. Sweet's syndrome and malignancy: report of the first case associated with adenocarcinoma of the lung. Lung Cancer 1993;10:95–9.
5. Yamamoto T, Furusue Y, Nishioka K. Sweet's syndrome with small cell carcinoma of the lung. J Dermatol 1994;21:125–7.
6. Cohen PR, Holder WR, Tucker SB, Kono S, Sci DM, Kurzrock R. Sweet syndrome in patients with solid tumors. Cancer 1993; 72:2723–31.
7. Kurzrock R, Cohen PR. Cutaneous paraneoplastic syndromes in solid tumors. A J Med 1995;99:662–71.
8. Dyall-Smith D, Billson V. Sweet's syndrome associated with adenocarcinoma of the prostate. Australas J Dermatol 1998;29: 25–7.
9. Smolle J, Kresbach H. Acute febrile neutrophilic dermatosis (Sweet syndrome) (in German with English abstract). Hautarzt 1990;41:549–56.

10. Weenig RH, Bruce AJ, McEvoy MT, Gibson LE, Davis MDP. Neutrophilic dermatosis of the hands: four new cases and review of the literature. Int J Dermatol 2004;43:95–102.
11. Denhove AV, Freymond N, Isaac S, Marrou K, Blame B, Gormand F, et al. Sweet's syndrome associated with squamous cell bronchial carcinoma. Neutrophilic dermatosis and non-small cell lung cancer (in French with English abstract). Rev Mal Respir 2007;24:77–80.