Abstract

Sweet’s syndrome is reportedly associated with preceding nontuberculous mycobacterial infections (NTMIs). Here, we report on a systemic *Mycobacterium intracellulare* infection in a patient on corticoid therapy for Sweet’s syndrome. Literature searches show that 69.1% of patients with Sweet’s syndrome and NTMIs developed this syndrome later than NTMIs and 89.3% of them developed during the clinical course of a rapidly growing mycobacterial infection. The residual cases were associated with slow-growing mycobacteria (14.3%), but only three cases of *Mycobacterium avium* complex (MAC) infections before the onset of Sweet’s syndrome have been reported, and all of them were caused by disseminated MAC disease. One of these cases developed during corticoid therapy for Sweet’s syndrome, while another case had underlying diabetes mellitus. Hence, the occurrence of systemic MAC disease may be an inevitable consequence of long-term steroid use and underlying diseases. Literature searches also showed that cervical lymphadenitis was a predominant symptom in NTMIs (90.5%). The present case did not have cervical lymphadenitis although the previously reported MAC cases did experience it. Therefore, lymphadenitis from NTMIs may be related to the pathogenesis of Sweet’s syndrome. Hence, should a patient have systemic infection without lymphadenitis, it will be more difficult to clinically confirm that MAC disease is a predisposing factor for Sweet’s syndrome.

Keywords: *Mycobacterium avium*, predisposing factor, Sweet’s disease

INTRODUCTION

Sweet’s syndrome is an acute febrile neutrophilic dermatosis characterized by recurrent, tender erythematous papules, or nodules infiltrated by neutrophils. The syndrome, which was originally described by Dr. Robert Douglas Sweet in 1964, is classified into three subtypes: classical Sweet’s syndrome, malignancy-associated Sweet’s syndrome, and drug-induced Sweet’s syndrome.[1] Classical Sweet’s syndrome can occur in a variety of medical conditions, but it most frequently occurs during infections in people with inflammatory bowel disease and in pregnancy.[2] This infection is particularly associated with upper respiratory tract and gastrointestinal infections, and under these circumstances, Sweet’s syndrome usually develops 1–3 weeks after the initial infection.[3] Sweet’s syndrome often presents itself during clinical infections with rapidly growing mycobacteria (RGM), but it rarely appears during the clinical infections with slowly growing mycobacteria (SGM).[4-7] However, the details concerning the relationship between Sweet’s disease and SGM are not well known. Here, we present a case report on a patient who developed Sweet’s syndrome secondary to an infection with slow-growing *Mycobacterium avium* complex (MAC). We also conducted a review of the related English literature through

Address for correspondence: Dr. Kenji Hibiya,
Department of Infectious, Respiratory, and Digestive Medicine, Control and Prevention of Infectious Diseases, Faculty of Medicine, University of the Ryukyu,
270 Uehara, Nishihara, Nakagami-gun, Okinawa 903-0215, Japan.
E-mail: kenjhibiya@gmail.com

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MEDLINE and present here our consideration of the relationship between both diseases (i.e., Sweet’s syndrome and MAC).

**Case Report**

A 71-year-old man with bone marrow failure syndrome presented to the local medical facility with preexisting dyspnea on exertion over several years [Table 1]. Chest radiographs indicated the presence of organizing pneumonia or eosinophilic pneumonia, but the patient neglected to follow-up. One year later, he was admitted to a different local medical facility with fever and cough presenting over 1 month. Chest radiography revealed the presence of bilateral ground-glass opacities and reticular shadows on the X-ray film. Tissue histology from a transbronchial lung biopsy (TBLB) indicated the presence of organizing pneumonia, and bacterial infection or lung cryptococcosis was suspected as possible causes. Antibiotics and antifungal agents were administered and his fever decreased, but the fever and wet cough often reoccurred. Antibiotics were administrated repeatedly.

Exanthema on his neck and a corresponding fever appeared during the clinical course, prompting his visit to the Department of Dermatology (University of Ryukyus Hospital, Japan). In this facility, skin biopsy showed classical dermal neutrophilic infiltration without vasculitis, a finding compatible with Sweet’s syndrome. Oral steroid therapy at 40 mg/day was started. Although the clinical response was good, skin eruption and a corresponding fever recurred when the steroid dose was tapered. He was then transferred to our department because of the abnormal chest radiography. The chest X-ray and computed tomography (CT) results indicated consolidation with volume loss in the right lower lobe [Figure 1a and b], suggesting organizing pneumonia or eosinophilic pneumonia.

Table 1: Clinical summary

| Timeline   | Clinical findings (diagnosis)                                                                 | Test results ⇒ Treatment/outcome                                                                 |
|------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| 2005       | Leucopenia (diagnosed as bone-marrow failure syndrome: ICUS)                                 | WBC 1,600 ⇒ maintenance therapy but neglected clinical follow-up                                  |
| 2011       | Dyspnea on exertion starting several years ago                                               | Abnormal shadow on chest CT-scan ⇒ neglected clinical follow-up                                  |
| 2012.5.13  | Fever and cough over 1 month                                                                 | Chest X-ray and CT indicated consolidation with volume loss in the right lower lobe                |
| 5.14       | Diagnosed as organizing pneumonia                                                          | TBLB showed OP pattern ⇒ antibiotics, antimycobacterial agents                                    |
| 6          | Advent of neck skin eruption                                                                | ⇒ PSL 40mg                                                                                       |
| 2012.7     | Diagnosed as Sweet’s syndrome on biopsy                                                     | ⇒ PSL 10mg-25mg                                                                                  |
| 8          | Recurrent fever and skin eruption after decreasing the prednisolone dose                     |                                                                                                   |
| 2013.5.13  | Work-up of abnormal chest x-ray [Figure 1 a, b]                                             | TBLB showed OP pattern ⇒ PSL up to 35mg                                                           |
| 2013.6.12  | Advent of fever in the 38°C region and wet cough                                            | ⇒ CAM, PSL 10mg-35mg                                                                             |
| 6.23       | Fever in the 40°C region and difficulty with eating and drinking                            | Chest X-ray and CT revealed bilateral patchy infiltrations with surrounding ground-glass opacities |
|            |                                                                                             | in both lower lobes ⇒ PSL up to 40mg; meropenem hydrate prescribed                                |
| 6.26       | Worsening of respiratory sign [Figure 1 c, d]                                              | Bronchoscopy performed but obtained only BALF for bleeding ⇒ PSL up to 70mg                       |
| 7.2        | Advent of persistent fever (38-39°C), worsening pancytopenia                                | Blood/feces/sputum culture                                                                        |
| 7.24       | Diagnosed as disseminated MAC                                                               | Bone marrow biopsy (AFB+) ⇒ RFP, EB, CAM                                                          |
|            | Since then                                                                                  | *Mycobacterium intracellulare* isolated from bone marrow, blood, feces, and sputum               |

AFB: Acid fast bacilli, BALF: Bronchoalveolar lavage fluid, CAM: Clarithromycin, CT: Computed tomography, EB: Ethambutol, ICUS: Idiopathic cytopenia of undetermined significance, MAC: *Mycobacterium avium* complex, OP: Organizing pneumonia, PSL: Prednisolone, RFP: Rifampicin, TBLB: Transbronchial lung biopsy, WBC: White blood cell count

Figure 1: Plain chest X-ray (a) and chest computed tomography image (b) from the initial admission to the University of the Ryukyus Hospital. Chest radiography showing consolidation with volume loss in the right lower lobe. Plain chest X-ray (c) and chest computed tomography image (d) on the second admission. Chest radiography showing the bilateral patchy infiltrations with surrounding ground-glass opacities in both lower lung lobes.
TBLB was performed and the histological findings from the biopsy specimens showed granulated tissues within alveolar ducts and mild alveolar septal thickening with lymphocyte infiltration and interstitial fibrosis. However, the neutrophilic infiltrations were scant [Figure 2]. Methenamine silver staining and Ziehl–Neelsen staining afforded negative results. Therefore, organizing pneumonia associated with Sweet’s syndrome was suspected. Prompt treatment with prednisolone (35 mg/day) improved the radiographic chest image. However, the patient’s fever and skin eruption both recurred when the prednisolone dose was tapered, and diffuse infiltrates emerged on the chest X-ray when prednisolone was tapered down to 10 mg/day. Therefore, the prednisolone dose was increased to 20–25 mg/day accordingly. The following year, the patient was readmitted to our department with fever (38°C) and a wet cough. We increased the prednisolone dose up to 35 mg/day, and the patient was discharged from the hospital with an improvement in his clinical condition.

Eleven days postdischarge, the patient was transferred back to us with fever (40°C), a wet cough, and difficulty eating and drinking. Chest X-ray and CT revealed bilateral patchy infiltrations with surrounding ground-glass opacities in both lower lung lobes [Figure 1c and d]. Prednisolone therapy was increased (up to 40 mg) and intravenous meropenem hydrate was prescribed. Three days later, his respiratory condition worsened, and a bronchoscopic examination was performed. TBLB was not performed because of bleeding, and the bronchoalveolar lavage showed nonspecific findings. Prednisolone therapy was increased (up to 70 mg) and an improvement in his clinical condition was observed, but a persistent fever (38°C–39°C) emerged, followed by pancytopenia. Bone marrow biopsy was performed and acid-fast bacilli were observed in the biopsied tissue. Mycobacterium intracellulare was cultured from the patient’s bone marrow, blood, feces, and sputum. Based on these results and his clinical course, we concluded that the pulmonary lesion was caused by a disseminated M. intracellulare infection. Rifampicin, ethambutol, and clarithromycin with steroids were administered, and his pulmonary lesions and respiratory signs and symptoms promptly improved in response to the antibiotic and steroid therapy. Later, immunohistological analysis revealed the presence of mycobacterial antigen in the tissue obtained from the second TBLB [Figure 3].

**DISCUSSION**

Sweet’s syndrome is reported to be associated with nontuberculous mycobacterial infections (NTMIs). Our review of the English-language literature found that 42 cases of Sweet’s syndrome in association with NTMIs have been reported through PubMed since 1992 [Table 2].[4-19] Most of these cases were associated with RGM [83.3%, Table 3]. The residual cases were associated with SGM (16.7%), but only four of them, including the present case, are associated with MAC [9.5%, Table 3]. This indicates that the most predominant causal agent is RGM, while MAC, which is slow growing, is a minor causal agent.[5]

In our literature review, the NTMIs most commonly associated with Sweet’s syndrome involved the cervical lymph nodes [90.5%, Table 3]. RGM cases commonly showed lymphadenitis [Table 2]. All SGM cases other than the present case also showed lymphadenitis [Table 2: Case 5, 8, 13, 36, 38, 41]. Thus, lymphadenitis may be a characteristic event in Sweet’s syndrome associated with NTMIs. In the present case, worsening of pancytopenia and immunosuppression by steroid treatment was observed after mid-2013 [Table 1]. Therefore, lymphadenitis might not be caused by a weakening of the host’s immune reaction. Interestingly, MAC is generally responsible for 80% of all nontuberculous mycobacterial lymphadenitis cases.[20] However, cervical lymphadenitis is less frequently observed in RGM infections, but these infections occur predominantly in skin and soft tissues following trauma and

**Figure 2:** Polypoid mass (Masson body) bulging outwards into the alveolar duct (*). Immature collagen fibers (red matter) were observed in the Masson bodies. Thickened alveolar septa with fibrosis were observed. Victoria Blue van Gieson staining (×200)

**Figure 3:** Mycobacterial antigens (brown matter) in epithelioid cells of the alveolar duct. (a) Low power microphotograph of immunohistochemical staining for mycobacterial antigens (×200). (b) A magnified image of the square in photo “a” (×600, bar indicates 10 µm)
Table 2: Non-tuberculous mycobacteriosis associated with Sweet’s syndrome

| Case | No. | Sex (country) | Site of involvement | Species isolated | Underlying diseases | Lesion histopathology | Onset of NTMI (onset of Sweet’s syndrome) |
|------|-----|---------------|---------------------|------------------|---------------------|----------------------|----------------------------------------|
| Wang, 2014[8]  | 1 | 51y/F (Thailand) | cervical LN, hilar LN, mediastinal LN, intraabdominal LN | *M. abscessus* | Anti-IFN-γ auto-Ab | granulomatous lymphadenitis | concurrent |
| Chan, 2013[9]  | 2 | 57y/M (China) | cervical LN | *M. chelonae* | Anti-IFN-γ auto-Ab | NS | preceding (1 week later) |
| 3 | 47y/F (China) | cervical LN, skin, axillary lymphadenopathies | *M. chelonae* | Anti-IFN-γ auto-Ab | granulomatous lymphadenitis | concurrent |
| Browne, 2012[10]  | 4 | 54y/NS (Thailand) | Disseminated NTMI | *M. abscessus* | Anti-IFN-γ auto-Ab | granulomatous lymphadenitis | concurrent |
| Kampitak, 2011[11]  | 5 | 56y/M (Thailand) | cervical LN, bone marrow, blood, intra-abdominal LN, retroperitoneal LN, anterior eye chamber, lung | *M. fortuitum* | Anti-IFN-γ auto-Ab | granulomatous lymphadenitis | preceding (1 month later) |
| 6 | 39y/M (Thailand) | cervical LN, inguinal LN, intraabdominal LN, blood, lymph nodes, skin | *M. abscessus* | Anti-IFN-γ auto-Ab | granulomatous lymphadenitis | concurrent |
| Sinawat, 2011[12]  | 7 | 47y/F (Thailand) | inguinal LN, amphibliesteode | RGM | NS | NS | following (NS) |
| Teraki, 2008[7] | 8 | 68y/F (Japan) | cervical LN, skin, spine | *M. avium* | NS | granulomatous lymphadenitis | preceding (1 month later) |
| Neoh, 2007[13] | 9 | 56y/F (Singapore) | cervical LNs | *M. chelonae* | HSV, Pul. TB | NS | NS |
| Chen, 2004[14] | 10 | 46y/F (Taiwan) | cervical LN | *M. fortuitum* | LCV | granulomatous lymphadenitis | following (NS) |
| Tuchinda, 2004[15] | 11 | 48y/F (Thailand) | cervical LN, bone | MCAC | NS | granulomatous lymphadenitis | preceding (1 year later) |
| 12 | 40y/M (Thailand) | cervical LN, liver, joints, inguinal LN | MCAC | NS | granulomatous lymphadenitis | preceding (6 weeks later) |
| 13 | 46y/F (Thailand) | cervical LN, lung, liver, spleen | *MAC* ⇒*M. chelonae* | diabetes mellitus | granulomatous lymphadenitis | preceding (2 months later) |
| 14 | 49y/M (Thailand) | cervical LN | *M. fortuitum* | NS | granulomatous lymphadenitis | preceding (2 months later) |
| 15 | 52y/F (Thailand) | cervical LNs, eyes | MCAC | NS | granulomatous lymphadenitis | preceding (2 months later) |
| 16 | 51y/F (Thailand) | cervical LN | MCAC | NS | granulomatous lymphadenitis | preceding (6 weeks later) |
| Theng, 2003[16] | 17 | 56y/F (China) | cervical LNs | *M. chelonae* | NS | NS | concurrent |
| Sungkanuparph, 2003[17] | 18 | 39y/F (Thailand) | cervical LNs | *M. chelonae* | NS | NS | NS |
| 19 | 47y/F (Thailand) | cervical LNs, bone | MCAC | NS | NS | NS |
| 20 | 52y/F (Thailand) | cervical LN | MCAC | NS | NS | NS |
| 21 | 40y/M (Thailand) | cervical LN, inguinal LN | MCAC | None (HIV negative) | granulomatous lymphadenitis | concurrent |
| Mahaisavariya, 2002[18] | 22 | 38y/F (Thailand) | cervical LN | *M. fortuitum* | NS (HIV negative) | granulomatous lymphadenitis | preceding (NS) |
| 23 | 44y/F (Thailand) | cervical LN, lung, sinus | *M. chelonae* | NS (HIV negative) | granulomatous lymphadenitis | preceding (NS) |
| 24 | 47y/F (Thailand) | cervical LN | *M. fortuitum* | NS (HIV negative) | granulomatous lymphadenitis | preceding (NS) |
| 25 | 49y/F (Thailand) | cervical LN, lung, liver | *M. fortuitum* | NS (HIV negative) | chronic granulomatous lesion | preceding (NS) |

Contd...
Table 2: Contd...

| Case | No. | Sex (country) | Site of involvement | Species isolated | Underlying diseases | Lesion histopathology | Onset of NTMI (onset of Sweet’s syndrome) |
|------|-----|---------------|---------------------|------------------|--------------------|----------------------|-----------------------------------------|
| Chetchotisakd, 2000[16] | 26 | 38y/M (Thailand) | cervical LN, tonsil, sinus, breast, skin, bone, joint | MCAC | NS (CD4:290) | epithelioid granuloma | preceding (NS) |
| | 27 | 35y/M (Thailand) | cervical LN | MCAC | NS (CD4: NS) | epithelioid granuloma | preceding (NS) |
| | 28 | 41y/F (Thailand) | cervical LN, sinus | MCAC | NS (CD4: 770) | epithelioid granuloma | preceding (NS) |
| | 29 | 31y/F (Thailand) | cervical LN, sinus, liver | M. abscessus | NS (CD4: 930) | epithelioid granuloma | preceding (NS) |
| | 30 | 41y/F (Thailand) | cervical LN, sinus, skin, liver, spleen | M. abscessus | NS (CD4: 730) | epithelioid granuloma | preceding (NS) |
| | 31 | 36y/M (Thailand) | cervical LN, lung | M. abscessus | NS (CD4: NS) | epithelioid granuloma | preceding (NS) |
| | 32 | 55y/M (Thailand) | cervical LN, lung | M. abscessus | NS (CD4: NS) | epithelioid granuloma | preceding (NS) |
| | 33 | 47y/M (Thailand) | cervical LN | M. abscessus | NS (CD4: 1,540) | epithelioid granuloma | preceding (NS) |
| | 34 | 51y/M (Thailand) | cervical LN | M. abscessus | NS (CD4: 1,320) | epithelioid granuloma | preceding (NS) |
| Choonhakarn, 1998[18] | 35 | 39y/F (Thailand) | cervical LN, bone, liver, spleen, sinuses | M. chelonae | NS | granulomatous lymphadenitis | preceding (NS) |
| | 36 | 30y/F (Thailand) | cervical LN, bone | M. scrofulaceum* | NS | granulomatous inflammation | preceding (NS) |
| | 37 | 41y/F (Thailand) | cervical LN | M. chelonae | NS | granulomatous inflammation | preceding (NS) |
| | 38 | 25y/F (Thailand) | cervical LN, joint, liver, spleen | MAC* | NS | granulomatous inflammation | preceding (NS) |
| | 39 | 35y/F (Thailand) | cervical LN, lung, brain stem | M. chelonae | NS | granulomatous inflammation | preceding (NS) |
| Hsiao, 1995[19] | 40 | 52y/F (Taiwan) | cervical LN | M. fortuitum | NS | NS | preceding (NS) |
| Kramers, 1992[20] | 41 | 40y/M (Netherlands) | Blood, mediastinal LN | M. kansasii* | hairy cell leukemia | NS | NS | concurrent |
| Present case | 42 | 71y/M (Japan) | Lung, bone marrow | M. intracellulare* | BMFS | organizing pneumonia | following (10 months later) |

Ab: Antibody, HSV: Herpes simplex virus, LCV: Leukocytoclastic vasculitis, LN: Lymph node, MAC: Mycobacterium avium complex, MCAC: M. chelonae/abscessus complex, BMFS: Bone marrow failure syndrome, NS: Not specified, NTMI: Non-tuberculous mycobacterial infection, Pul. TB: Pulmonary tuberculosis, RGM: Rapidly growing mycobacteria, y: year, CD4 count: cells/μL. *Asterisks indicate slowly growing mycobacteria

after surgical or other procedures in patients without underlying complicated diseases.[21,22] An explanation for this discrepancy has not been established.

In this literature review, the SGM cases showed commonality in their systemic mycobacterial infections [Table 2]. In the present case, systemic M. intracellulare infection developed during corticosteroid therapy for Sweet’s syndrome, but the patient did not initially show an obvious local infection during the clinical course. Therefore, the M. intracellulare infection in this patient is thought to have been caused by corticosteroid immunosuppression, as has been shown in the MAC infection cases reported previously [Table 2: cases 8 and 13]. One of the cases reported previously (Case 8) emerged during corticosteroid therapy for Sweet’s syndrome,[71] while the remaining case (Case 13) had underlying diabetes mellitus.[15] Immunocompromised hosts are readily colonized by opportunistic SGM.[23,24] Sweet’s syndrome patients are susceptible to infection as a result of their underlying disease state (e.g., hematological malignancy and autoimmune disorders) and by the systemic steroid therapy used to treat this syndrome. In fact, the rate of systemic infection is over 50% for all the NTMI cases [Tables 2 and 3]. Hence, MAC might not be a preceding factor for Sweet’s syndrome as long as the infection develops after its onset.

The literature shows that subcutaneous lesions associated with Sweet’s syndrome have been reported following NTMI; however, none of the reports has detailed the date of occurrence of Sweet’s syndrome, chronologically. Therefore, we determined the date when the NTMI first occurred in the cases with Sweet’s syndrome in chronological order [Figure 4]. Our results identified 28 cases (69.1%) where NTMI occurred before the onset of Sweet’s syndrome,

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Table 3: Characteristics of the 42 reported cases

| Characters | Finding data |
|-----------|--------------|
| Age, years: | Median (Range) 47 (25-71) |
| Gender (%) | Men, 14 (33.3); Women, 27 (64.3); not specified, 1 (2.4) |
| Country (%) | Thailand, 33 (78.6); Taiwan, 2 (4.8); China, 3 (7.1); Japan, 2 (4.8); Netherlands, 1 (2.4); Singapore, 1 (2.4) |
| Involvement (%)* | Cervical lymph nodes, 38 (90.5); lung, 8 (19.1); systemic, 21 (50.0) |
| Mycobacteria isolated (%) | Total-RGM, 35 (83.3); Total-SGM, 7 (16.7); not specified NTM, 1 (2.4) |
| Underlying disease | Anti-IFN-γ auto-antibody, 6 (14.3); HSV, 1 (2.4); LCV, 1 (2.4); diabetes mellitus, 1 (2.4); HCL, 1 (2.4); BMFS, 1 (2.4); none, 1 (2.4); not specified, 30 (71.4) |
| Onset of Sweet’s syndrome (%) | Preceding, 28 (69.1); Concurrent, 6 (14.3); Following, 3 (7.1); not specified, 5 (11.9) |

NTM: Non-tuberculous mycobacteria, MAC: Mycobacterium avium complex, RGM: Rapid growing mycobacteria, SGM: Slow growing mycobacteria, HSV: Herpes simplex virus, LCV: Leukocytoclastic vasculitis, HCL: Hairy cell leukemia, BMFS: Bone marrow failure syndrome

6 cases (14.3%) where it was acquired concurrently with NTMI, and 3 cases (7.1%) where it occurred later than the onset of Sweet’s syndrome [Table 3 and Figure 4]. Cases of Sweet’s syndrome occurred within 12 months of NTMI, and most cases occurred within 2 months of it [Figure 4]. Thus, NTMI predominantly precedes the onset of Sweet’s syndrome, possibly indicating that NTMI is likely to be a trigger for the development of this syndrome.

We wanted to confirm that there was no possibility that an MAC infection was already established before the onset of Sweet’s syndrome in the present case, which showed organizing pneumonia from the earliest days of the clinical course. The results of the second transbronchial-biopsied tissue reported that Mycobacterium antigen was under review. This indicates that the patient was infected with MAC before the diagnosis of MAC disease. However, we could not confirm that the causative agent of the initial organizing pneumonia was present before the onset of Sweet’s syndrome. A few cases of MAC-associated organizing pneumonia have been reported. Organizing pneumonia often responds well to corticosteroid therapy. Therefore, it is entirely possible that the pulmonary infection was masked by the corticosteroid therapy. In addition, the present case presented a lesion in the middle lobe/lingular lung segment. Bacterial colonization of this site occurs readily because, anatomically, the middle lobe and lingular segment have low clearance. M. avium can form biofilms in the bronchiolar and bronchial mucosa, raising speculation that in the present patient, M. intracellularare had colonized the organized lesion.

Table 4 and Figure 4 show the data, including the number of cases and their corresponding date of diagnosis. Figure 4a depicts the chronological evaluation of the onset of NTMI in the reported 42 cases of Sweet’s syndrome. (a) Rough chronological evaluation of the onset of NTMI in patients with Sweet’s syndrome. (b) The evaluation of the onset of NTMI in patients with Sweet’s syndrome on a monthly basis. Note, however, that 16 of the 42 cases had an obvious date of concurrence. The filled square and circle represent the present case.

61 cases [22,28,29] of non-tuberculous mycobacterial infections (NTMI) in the reported 42 cases of Sweet’s syndrome. The involvement of the head and neck for any Sweet’s syndrome category is over 50%. In addition, Sweet’s syndrome is accompanied by pharyngeal pain as a predominant symptom. These findings indicate the possibility of the tonsils being the focal point of infection and the etiological agents include RGM.

Figure 4: Chronological evaluation of the onset of non-tuberculous mycobacterial infections (NTMI) in the reported 42 cases of Sweet’s syndrome. (a) Rough chronological evaluation of the onset of NTMI in patients with Sweet’s syndrome. (b) The evaluation of the onset of NTMI in patients with Sweet’s syndrome on a monthly basis. Note, however, that 16 of the 42 cases had an obvious date of concurrence. The filled square and circle represent the present case.

Literature searches show that erythematous lesions in Sweet’s syndrome appear primary in the upper extremities (head and neck), and lower extremity lesions are infrequent. The involvement of the head and neck for any Sweet’s syndrome category is over 50%. In addition, Sweet’s syndrome is accompanied by pharyngeal pain as a predominant symptom. These findings indicate the possibility of the tonsils being the focal point of infection and the etiological agents include RGM.

Sweet’s syndrome is often associated with immune disorders involving anti-interferon gamma (IFN-γ) autoantibodies, as well as bone marrow dysplasia and auto-inflammatory diseases [Table 2]. However, it is not known exactly how they affect the onset of erythematous lesions in Sweet’s syndrome.
syndrome. Sweet’s syndrome is generally regarded as a hypersensitive reaction to bacteria, viral, or tumor antigens. Inappropriate secretion of endogenous chemokines and cytokines against such antigens may contribute to the initiation and propagation of the inflammatory response in Sweet’s syndrome.\(^{[39]}\) Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) have been implicated in granulocyte activation and they enhance the function of mature neutrophils.\(^{[40,41]}\) In patients with Sweet’s syndrome, serum type 1 helper T-cell (Th1) cytokine levels including interleukin (IL)-1\(\beta\), IL-1\(\alpha\), IL-2, and IFN-\(\gamma\) are elevated, whereas type 2 helper T cell (Th2)-related cytokine IL-4 levels remain normal.\(^{[42]}\) Reuss-Borst et al. reported that IL-6 and G-CSF serum levels were maximally high during the acute phase of the disease, but IL-1\(\beta\) and IFN-\(\gamma\) serum levels were not elevated.\(^{[43]}\) Marzano et al. reported that tumor-necrosis-factor (TNF)-\(\alpha\) was moderately high and that IL-8 and IL-17 were slightly high in Sweet’s syndrome patients compared with the same values in normal controls.\(^{[44]}\) Thus, the cytokine secretion pattern during the immune response in Sweet’s syndrome differs in each study. We consider that the secretion pattern may be dictated by the preceding causal agent and the immune status of the host. For example, the Th1-type immune response (IL-1\(\alpha\), IL-12, GM-CSF, and TNF-\(\alpha\)) is predominant following mycobacterial infection.\(^{[45-48]}\) Mycobacterium chelonae (categorized as RGM) induces IL-8 from macrophages.\(^{[49]}\) It is known that immunity in immunocompromised hosts shifts to a Th2-type response. Therefore, NTMIs preceding Sweet’s syndrome may induce a dominant Th1-type immune response and the established immunological deterioration may induce dominance in Th2-type immunity during the clinical course of Sweet’s syndrome.

**Conclusion**

The occurrence of systemic MAC disease may be an inevitable consequence of long-term steroid use and the presence of underlying diseases (e.g., hematological malignancy such as myelodysplastic syndrome, other malignancies, and anti-IFN-\(\gamma\) autoantibodies). If the appearance of MAC disease is lymphadenitis, it will be clinically straightforward to confirm that MAC disease is a contributing factor in Sweet’s disease. Cervical lymphadenitis caused by MAC and local infection with RGM often develops in the absence of impaired immunity. However, if the appearance is systemic infection, it will be difficult to clinically confirm that MAC disease is a contributing factor in Sweet’s syndrome.

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**Conflicts of interest**

There are no conflicts of interest.

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