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Case Report

Heerfordt's Syndrome Associated with a High Fever and Elevation of TNF-α

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Heerfordt's syndrome is a rare manifestation of sarcoidosis and is defined as a combination of facial palsy, parotid swelling, and uveitis, associated with a low-grade fever. We report a case of Heerfordt's syndrome presenting with a high fever and increased serum tumor necrosis factor alpha (TNF-α) levels. The patient had facial palsy, parotid swelling, uveitis, and swelling of the right supraclavicular and hilar lymph nodes. Corticosteroid therapy was initiated, and her symptoms soon resolved completely, in tandem with a decrease in TNF-α serum levels.

Key words: Heerfordt's syndrome, sarcoidosis, TNF-α

Heerfordt's syndrome falls within the spectrum of sarcoidosis, and occurs in 2–5% of all sarcoidosis cases [1, 2]. It is defined as a combination of facial palsy, parotid swelling, and uveitis, usually associated with a low-grade fever [3]; cases that involve all three symptoms are called "complete Heerfordt's syndrome" [4]. Heerfordt's syndrome manifests in various forms, and cases of complete Heerfordt's syndrome are extremely rare.

Tumor necrosis factor (TNF-α) is thought to be critical in the genesis and maintenance of granulomatous inflammation, and a case of refractory sarcoidosis that responded to infliximab (an anti-TNF-α antibody) has been reported [5]. Here, we report a unique case of complete Heerfordt's syndrome with a high fever that presented with elevated serum TNF-α levels. Following corticosteroid treatment the symptoms, including the fever, were improved and were found to be associated with decreased TNF-α levels, suggesting that TNF-α levels were correlated with the disease activity of complete Heerfordt's syndrome. The literature from 2005 to 2015 in the MEDLINE database was also reviewed, based on a search for Heerfordt's syndrome and its clinicopathological presentations.

Case Report

A 34-year-old woman was referred to our hospital to evaluate blurred vision and right facial palsy. She had a history of external hemorrhoids and an ovarian cyst with no noteworthy findings in her family history. She smoked one pack of cigarettes per day for 15 years until age 31 and drank alcohol socially. She had a 16-day history of blurred vision, which had been diagnosed as uveitis and treated at another hospital with antibiotics and a corticosteroid ophthalmic solution. After 6 days of treatment, she developed a right-sided facial palsy, which was diagnosed as Bell's palsy and treated with oral steroids, tapered over ten

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days (Betamethasone 3 mg for 2 days, 2 mg for 2 days, 1.5 mg for 2 days, 1 mg for 2 days, 0.5 mg for 2 days). However, her symptoms improved only partially.

On physical examination, she was found to have uveitis and House-Brackmann grade III right peripheral facial nerve palsy. Her parotid glands were swollen bilaterally, and solid and painful to touch. Her light supraclavicular lymph node was palpable. An examination of her lungs and heart was normal, as were other cranial nerve, motor, and sensory nerve examinations. Her serum lysozyme (14.8 μg/mL; normal range: 4.2–11.5 μg/mL), soluble IL-2 receptor (1,141 IU/mL; normal range: 124–466 IU/mL), and TNF-α levels (141 pg/mL; normal range: $<$2.8 pg/mL) were elevated. Her serum angiotensin-converting enzyme, serum, and urinary calcium levels were all within normal limits. Chest computed tomography (CT) revealed bilateral parotid gland swelling, right supraclavicular, mediastinal, and hilar lymphadenopathy, which accumulated gallium during scintigraphy (Fig. 1).

Five days after the patient arrived at our hospital, a percutaneous needle biopsy of her supraclavicular lymph node was performed, which revealed non-suppurative granulomatous lymphadenitis. She developed a fever of over 38.0℃. Seven days later, her mediastinal lymph node was biopsied via endobronchial ultrasound-guided transbronchial needle aspiration, and this also revealed non-suppurative granulomatous lymphadenitis (Fig. 2). Furthermore, bronchoalveolar lavage fluid revealed an elevated CD4/CD8 ratio (8.53), which supported the diagnosis of sarcoidosis of the lung.

Complete Heerfordt's syndrome was diagnosed and the patient was started on corticosteroid therapy with oral prednisolone at 30 mg per day. The following day, her body temperature had recovered to normal levels, and within 2 weeks her blurred vision and right facial palsy had resolved completely. The serum TNF-α levels decreased to 28.1 pg/mL on day 57, and soluble IL-2 receptor, lysozyme decreased to 319 IU/mL, 8.3 μg/mL on day 120. The prednisolone dose was reduced to 15 mg for 3 months with no recurrence of symptoms.

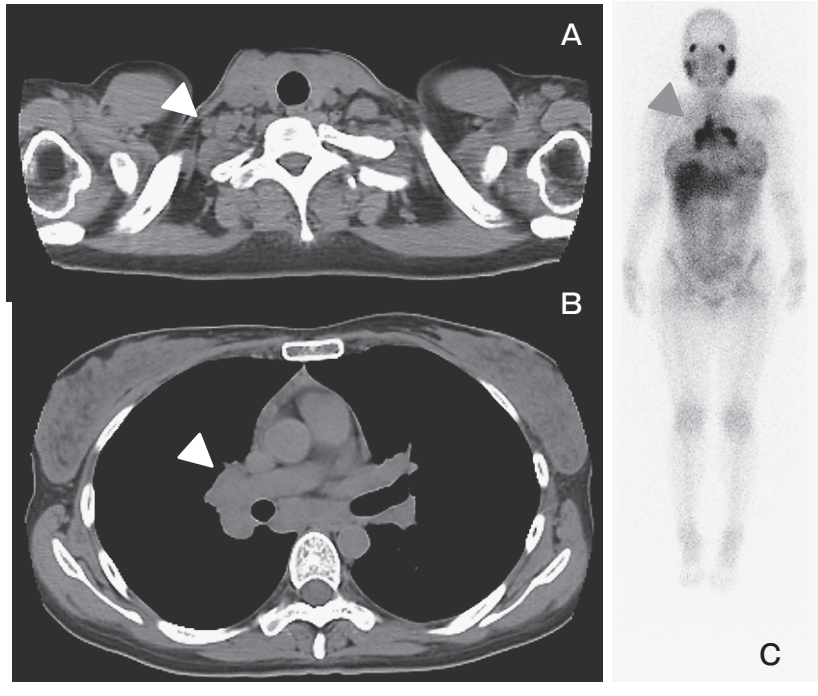

Fig. 1 Chest computed tomography revealed bilateral parotid gland swelling, and right supraclavicular (A), mediastinal, and hilar lymphadenopathy (B), which displayed a high accumulation of gallium during scintigraphy (C).

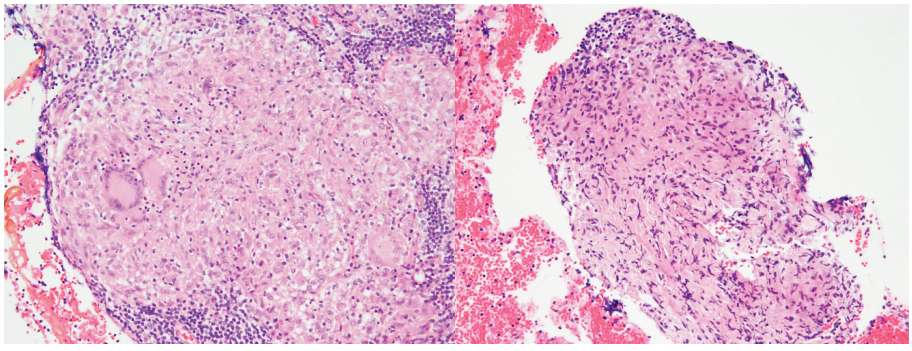

Fig. 2 A needle biopsy of the right supraclavicular lymph node (A) and an endobronchial ultrasound-guided transbronchial needle aspiration for the mediastinal lymph node (B) both revealed non-suppurative granulomatous lymphadenitis.

Discussion

Heerfordt's syndrome was first described in 1909 by the Danish ophthalmologist Christian Fredrick Heerfordt [3]. This syndrome is a combination of uveitis, parotid gland enlargement, and facial nerve palsy, usually associated with a low-grade fever. In 1938, Bruins-Slot *et al.* determined that this syndrome was associated with sarcoidosis [4], and called cases that presented with all three symptoms and a low-grade fever "complete Heerfordt's syndrome". Darlington *et al.* analyzed the manifestations of sarcoidosis and reported that among 1,000 sarcoidosis patients, only 3 (0.3%) had complete Heerfordt's syndrome [6].

Our case had complete Heerfordt's syndrome, presenting with a high fever instead of a low-grade fever. Serum TNF-α levels appeared to be correlated with the disease activity, since the increased TNF-α levels decreased following corticosteroid treatment, in tandem with improvements in her symptoms, including her high fever. There has been one reported case of complete Heerfordt's syndrome with increased serum TNF-α levels [7]. In that report, similar to our case, the serum TNF-α level was over 100 pg/mL (136 pg/mL), and tended to be higher than in general sarcoidosis cases (mean 26.3 pg/mL, n = 8). To our knowledge, our case is the first report of complete Heerfordt's syndrome in which the serum TNF-α levels were evaluated both before and after corticosteroid therapy.

To analyze the various presentations of Heerfordt's syndrome, a search of the MEDLINE database of literature published between 2005 and 2015 yielded 30 articles. After excluding those articles not specifically related to Heerfordt's syndrome, 19 articles (21 cases including our case) were reviewed [7–25] (Table 1). The median patient age was 32 (range 14–59) years and there were 10 males and 11 females. Twelve cases were described as complete Heerfordt's syndrome. Out of the 21 cases, only 4 presented with a fever > 38℃ (Table 1–1). Eight cases were initially diagnosed with another disease: Bell's palsy, temporomandibular joint disorder, parotitis, hay fever, Guillain-Barre syndrome, and Sjögren's syndrome. Most of the cases were treated with corticosteroids and the clinical symptoms improved, to some extent (Table 1–2).

TNF-α is thought to generate a fever via the production of prostaglandin E_2 in the hypothalamus. Sweiss *et al.* reported significant associations of TNF-α and type I interferon serum levels with clinical manifestations in a sarcoidosis cohort. They reported that in African-Americans, the TNF-α levels were higher in those cases with sarcoidosis and a neurological disease, compared to those patients with sarcoidosis alone [26]. The TNF-α levels were very high in our case, and improved quickly following corticosteroid therapy. Therefore, since the association of fever and neurological symptoms with the serum TNF-α level in sarcoidosis has been reported, serum TNF-α is a possible biomarker for disease activity in Heerfordt's syndrome. Recently, TNF-α antagonists have been reported to advance the treatment of inflammatory arthropathies, and are even considered for use in refractory sarcoidosis, with some success [5]. Para-

Table 1-1 Literature review of the Heerfordt's syndrome cases and their clinical findings

No.	Year	Authors	Country	Age	Sex	Clinical Type	Facial palsy	Uveitis	Parotid swelling	Fever	Onset
1	2005	Walter *et al.*	Germany	50	F	Complete	BL	+	BL	−	parotid swelling
2	2005	Braido *et al.*	Italy	34	M	Incomplete	−	ND	BL	ND	facial hyperesthesia
3	2005	Blair *et al.*	USA	44	M	Incomplete	−	+	BL	+	fever
4	2006	Ishimatsu *et al.*	Japan	27	M	Complete	Right	+	Right	++	blurred vision
5	2006	Ishiwata *et al.*	Japan	28	M	Complete	Right	+	BL	+	myodesopsia
6	2007	Ueda *et al.*	Japan	51	F	Incomplete	Left	+	−	ND	facial palsy
7	2007	Tamme *et al.*	Estonia	22	F	Incomplete	Right	−	BL	−	parotid swelling
8	2008	Petropoulos *et al.*	Switzerland	29	M	Complete	Left	+	BL	+	blurred vision/fever
9	2010	Yagi *et al.*	Japan	34	M	Incomplete	−	+	BL	+	fever/uveitis/parotid swelling/skin eruption
10	2010	Shimizu *et al.*	Japan	25	F	Complete	Right	+	BL	++	fever/parotid swelling
11	2011	Kato *et al.*	Japan	28	F	Complete	Right	+	BL	+	facial palsy
12	2012	Feiß *et al.*	Germany	14	M	Complete	Right	+	BL	++	photophobia
13	2013	Otani *et al.*	Japan	39	F	Incomplete	−	+	BL	+	blurred vision
14	2013	Feiß *et al.*	Germany	14	M	Complete	UL	+	BL	+	sinusitis
15	2013	Dua *et al.*	USA	32	F	Incomplete	Right	−	BL	−	parotid swelling
16	2013	Fukuhara *et al.*	Japan	22	M	Incomplete	−	+	BL	+	parotid swelling
17	2013	Fukuhara *et al.*	Japan	36	F	Incomplete	−	+	BL	+	parotid swelling
18	2013	Denny *et al.*	USA	59	F	Complete	Left	+	BL	+	fever
19	2014	Hirai *et al.*	Japan	30	M	Complete	BL	+	BL	+	fever
20	2015	Chappity *et al.*	India	52	F	Complete	BL	+	Left	+	facial palsy
21	2015	Current case	Japan	34	F	Complete	Right	+	BL	++	blurred vision

F, female; M, male; BL, bilateral; ND, not described: Fever +, low-grade fever; ++, high fever.

Table 1-2 Literature review of the Heerfordt's syndrome cases and their clinical findings

No.	Cytology (NCG site)	Initial Diagnosis	Treatment Interval	Therapy	Outcome	Recurrence
1	Parotid	sarcoidosis	ND	ND	ND	ND
2	ND	sarcoidosis	ND	steroid	Completely Improved	−
3	Parotid	sarcoidosis	3 months	PSL 30 mg	Completely Improved	−
4	TBLB	sarcoidosis	1.5 months	PSL 30 mg	Partially Improved	+
5	Parotid	sarcoidosis	2 months	PSL 30 mg	Partially Improved	−
6	TBLB	sarcoidosis	6 months	no therapy	Completely Improved	−
7	Lip	Sjögren's syndrome	ND	steroid	Completely Improved	−
8	TBNA	sarcoidosis	ND	PSL + AZA	Completely Improved	−
9	Skin	sarcoidosis	13 years	PSL 15 mg	Not Improved	−
10	TBLB	Bell's palsy	10 months	PSL 30 mg	Partially Improved	+
11	None (Clinical diagnosis)	Guillain-Barre syndrome	1.5 months	mPSL 500 mg	Partially Improved	+
12	Parotid	sarcoidosis	ND	PSL 75 mg	Completely Improved	−
13	Parotid	hay fever	3 months	PSL 30 mg	Completely Improved	−
14	Turbinectomy specimen	sarcoidosis	ND	ND	ND	ND
15	Parotid	sarcoidosis	1.5 months	PSL 60 mg	Completely Improved	−
16	TBLB	parotitis	1.5 months	PSL 50 mg	Completely Improved	−
17	TBLB	Temporomandibular joint disorder	ND	PSL 40 mg	Completely Improved	−
18	Pre-auricular LN	sarcoidosis	4 months	PSL	Completely Improved	−
19	Lip	sarcoidosis	3 months	mPSL pulse	Partially Improved	+
20	Parotid	Bell's palsy	4 months	PSL	Partially Improved	−
21	TBNA	Bell's palsy	1 months	PSL 30 mg	Completely Improved	−

NCG, non-caseating epithelioid granuloma; TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration; ND, not described; PSL, prednisolone; mPSL, methyl prednisolone; AZA, azathioprine.

doxically, however, cases of new-onset sarcoidosis-like diseases have also been reported in patients receiving TNF-α antagonists [27]. Therefore, careful consideration should be given to this risk when proposing TNF-α antagonists for refractory sarcoidosis.

In conclusion, we reported a case of complete Heerfordt's syndrome presenting with a high fever, in which elevated serum TNF-α levels decreased after corticosteroid therapy.

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