Kikuchi’s Disease: A Rare Cause of Meningitis?

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We present a case of Kikuchi’s disease causing meningitis associated with fever and treated successfully with corticosteroids alone. This is considered to be rare but provides an instructive example of how the diagnosis may be confused with that of tuberculous meningitis and highlights the importance of histopathological analysis.

Kikuchi’s disease is an idiopathic illness, typically causing cervical lymphadenopathy that is frequently associated with fever and generally resolves spontaneously over a 1–4 month period [1]. In addition to a range of other less common clinical manifestations, aseptic meningitis has been reported in cases of Kikuchi’s disease; of interest, such cases have been reported almost exclusively in Japanese patients [2]. Because it is mostly self-limiting and may be corticosteroid responsive, the disease can frequently be misdiagnosed, which can lead to inappropriate treatment. Many patients with Kikuchi’s disease who present with fever and meningitis will be assessed by infectious disease physicians who will not be aware of the association of Kikuchi’s disease with meningitis. This case report illustrates how Kikuchi’s disease, presenting in this way, can be mistaken for tuberculous meningitis, particularly when adjuvant corticosteroids are used in treating tuberculous meningitis.

Case report. A 37-year-old woman presented to our hospital (Northwick Park Hospital, Middlesex, United Kingdom) with a 2-week history of progressive headache associated with fever and nausea. She was ethnically South Asian, was born in Uganda, and had resided in the United Kingdom for 30 years. She had no significant medical history other than an acute febrile illness with tender cervical lymphadenopathy that was attributed to a viral infection and which occurred just before the onset of her headache. At admission, she had a temperature of 39°C and bilateral tender cervical lymphadenopathy with multiple nodes measuring 2–3 cm in diameter. During the subsequent 2 days, her headache deteriorated and was associated with photophobia and neck stiffness. She had a normocytic anaemia (hemoglobin level, 9.8 g/dL) and was leukopenic (2.8 × 10^9 cells/L) but had a normal differential cell count. Her C-reactive protein level was 110 mg/L, and the erythrocyte sedimentation rate was 94 mm in the first hour. The results of serological tests for HIV, Epstein-Barr virus, cytomegalovirus, toxoplasma, Bartonella species, treponema, and acute streptococcal infection were negative, as were the results of tests for autoantibodies, including antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibody. The result of a 10U Mantoux test was anergic, and the findings of a gadolinium-enhanced MRI scan of the brain were normal. A lumbar puncture, performed on the second day of hospitalization, demonstrated CSF with an opening pressure of 20 cm of water, a CSF:plasma glucose ratio of 0.65, an elevated protein level of 0.71 g/L, and a WBC count of 30 cells/μL (mainly mononuclear leucocytes). The patient’s fever persisted, and her meningitic symptoms deteriorated, leading to an additional lumbar puncture 2 days later. The opening pressure had increased to 35 cm of water, the protein level had increased to 1.83 g/L, the leucocyte count had increased to 75 mononuclear cells/μL, and the CSF:plasma glucose ratio had decreased to 0.47. In view of the patient’s ethnic origin, the possibility of tuberculous meningitis was considered. The progressive CSF changes were thought to be consistent, although her relatively acute presentation, negative Mantoux reaction, and relatively normal CSF glucose level were somewhat unusual for—but not incompatible with—a diagnosis of tuberculous meningitis. Empirical treatment for tuberculous meningitis was started without the addition of corticosteroids. However, a lymph node biopsy that was performed at this time showed features of Kikuchi’s lymphadenitis. This comprised an expanded B cell area with reactive lymphoid follicles. The T cell area was severely expanded, with numerous CD3- and CD8-positive transformed lymphocytes and fewer CD3- and CD4-positive lymphocytes. Within the expanded paracortex were multiple areas of extensive apoptosis with nuclear fragmentation and phagocytosis. The apoptotic cells had hematoxylin and eosin stain findings that were positive for CD68 and CD123 and negative for BCL-2. Scattered histiocytic cells showing myeloperoxidase positivity were also present. These findings are classical of Kikuchi’s lymphadenitis (figure 1).
Kikuchi’s lymphadenitis is normally considered to be self-limiting, and gradual recovery is expected over several weeks or months. However, in view of the progressive features and debilitating symptoms in our patient, we elected to treat her with prednisolone administered at a dosage of 80 mg/day and to stop antituberculous chemotherapy. Her fever and meningitic symptoms resolved quickly over the subsequent 48 h, and her CSF sample was normal when an additional lumbar puncture was performed 7 days later. The results of PCR testing of CSF samples for enteroviruses, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus were negative for all 3 samples. The patient’s lymphadenopathy improved over the subsequent 3–4 weeks. The dosage of steroid medication was gradually reduced over an 8-week period, and the patient remained well during an 8-month follow-up period.

Discussion. Kikuchi’s disease represents a histopathological diagnosis of lymphadenitis caused by hyperplastic changes with an abundance of apoptotic plasmacytoid monocytes and phagocytic histiocytes [1]. The major case series have been reported in Japanese and other Asian populations, typically affecting people 30–50 years old, with a modest female preponderance [3–5]. It has since been reported among many ethnic groups, and any perceived association with individuals of Asian ethnicity may be due, in part, to a greater awareness of this diagnosis among their physicians. The etiology of the disease is not known, but the strongest clinical and pathological association is with connective-tissue diseases, particularly systemic lupus erythematosus, which may precede, present concurrently with, or follow after Kikuchi’s disease [6, 7]. Associations with a variety of infections have also been proposed, but a causal relationship has not been proven [1].

Cervical lymphadenopathy affects 56%–98% of patients with Kikuchi’s disease. Importantly, up to 50% of these patients have fever and therefore attract the attention of infectious disease physicians. Noncervical regional lymphadenopathy, diverse dermatological manifestations, hepatosplenomegaly and constitutional features, such as weight loss and night sweats, are also recognized [1, 3, 4, 8]. Cases of Kikuchi’s disease associated with aseptic meningitis have been reported. One such report provides a useful summary of the characteristics of 11 Japanese cases from the literature [2]. These patients were 8–38 years in age with equal gender distribution. They had a subacute presentation evolving over a 2–6 week period with prominent headache, CSF opening pressure of 15–30 cm of water, mononuclear cell CSF pleocytosis of 49–1685 cells/µL, CSF protein levels of 0.26–2 g/L, and CSF:serum glucose ratios of 0.32–0.6. Like most reported cases of Kikuchi’s disease, these cases resolved spontaneously without any treatment 2–6 weeks after presentation.

The clinical and CSF features of these patients at presentation are clearly similar to those of patients with tuberculous meningitis, representing an infection that is endemic in South Asian and African populations and may also cause lymphadenopathy. The unequivocal diagnosis or exclusion of tuberculous meningitis, however, can be extremely difficult. Recently published diagnostic rules using clinical and basic laboratory characteristics of CSF, with 79% specificity in an adult population with a high prevalence of tuberculosis [9], will not distinguish Kik-
Kikuchi’s disease meningitis. Similarly, tuberculin skin tests, imaging, and examination of CSF samples with conventional bacteriological or molecular diagnostic tests may have poor sensitivity or specificity [10]. Therefore, the diagnosis of tuberculous meningitis is often presumptive and dependent on a therapeutic response to treatment. This treatment would often include corticosteroids, the use of which has recently been validated and reinforced by a randomized, placebo-controlled trial [11]. However, the inclusion of corticosteroids in the treatment regimen for tuberculous meningitis clearly may lead to nonspecific therapeutic effects in a wide range of inflammatory conditions. These include Kikuchi’s disease, for which corticosteroids, even at low doses, have been used to shorten the duration of illness or alleviate debilitating symptoms [12]. Spontaneous or corticosteroid-induced recovery of patients with Kikuchi’s disease meningitis may therefore be mistakenly interpreted as a therapeutic response to treatment for tuberculosis.

The distinction between Kikuchi’s disease and tuberculosis is not simply academic, however. Antituberculous chemotherapy can be toxic, which is cogently illustrated by a case report of fulminant hepatic failure as a result of empirical tuberculosis therapy in a patient with Kikuchi’s disease [13]. Furthermore, Kikuchi’s disease has rarely been associated with fatalities [1], and we have used intravenous immunoglobulin to successfully treat a patient with severe, steroid-resistant disease [14]. Therefore, the diagnosis of Kikuchi’s disease may provide other therapeutic opportunities for patients with severe disease that would otherwise be overlooked as the result of a presumptive diagnosis of tuberculous meningitis.

Cytological examination of samples obtained with fine-needle aspiration is often used as the initial tissue-sampling procedure in patients with lymphadenopathy, and cytological features in Kikuchi’s disease have been reported [15, 16], but histological examination is still required to make a diagnosis. Therefore, performance of a lymph node biopsy is a critical investigation in this clinical situation, especially for the purpose of distinguishing Kikuchi’s disease from tuberculous meningitis.

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References