

Follicular Thyroid Carcinoma Concurrent with Kikuchi-Fujimoto Disease: A Case Report and Literature Review

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1. Abstract

1.1. Background: Kikuchi-Fujimoto disease (KFD), also called histiocytic necrotizing lymphadenitis, is a rare, self-limited disease of unknown etiology. It is usually characterized by unilateral cervical lymphadenopathy, which can mimic lymph node metastasis.

1.2. Case Presentation: We report a case of follicular thyroid carcinoma concurrent with KFD. A 57-year-old female received sequential neck surgery to complete thyroidectomy for her incidentally diagnosed follicular thyroid carcinoma. Neck ultrasound was conducted to evaluate residual tumor burden before radioiodine therapy. Lymph node metastasis was suspected due to malignant sonographic features with hyperechoic content, the absence of hilum and hyper vascularity. Even negative cytology and undetectable thyroglobulin in the lymph node aspirate, this patient received neck lymph node dissection and then documented KFD.

1.3. Conclusion: Thyroid cancer with concurrent KFD is very uncommon. Nevertheless, it should be taken into consideration in patients with follicular thyroid carcinoma with lymphadenopathy. Lymph node aspirate for cytology and thyroglobulin measurement may provide valuable evidence to exclude a diagnosis of lymph

node metastases.

2. Introduction

Kikuchi-Fujimoto disease (KFD), also called histiocytic necrotizing lymphadenitis, is generally associated with fever, sweating and progressive painful lymphadenopathy in the cervical region. KFD, initially described in Japanese females in 1972, is rare and most reports are from Asia [1]. In Taiwan, KFD has been reported to account for 5.7% of all diagnoses among pathological specimens of abnormal lymph nodes [2]. Cervical lymphadenopathy over the posterior triangle is the most common (60-90%) presentation, associated with low-grade fever (35-77%) [1]. An optimal specimen from lymph node biopsy is essential for diagnosis of KFD because of the challenging differential diagnosis with other lymphadenopathies including infectious lymphadenitis of various etiologies (such as viruses or bacteria), autoimmune diseases such as Sjögren's syndrome or Systemic Lupus Erythematosus (SLE) related lymphadenopathy, and lymphoproliferative diseases like non-Hodgkin lymphoma [1, 3, 4]. Most patients are younger than 40 years old and are free of previous systemic diseases. KFD concurrent with thyroid cancer has been seldom mentioned. Here, we

report a case of KFD mimicking lymph node metastasis in a patient with follicular thyroid carcinoma after total thyroidectomy.

3. Case Report

A 57-year-old female was treated by left subtotal thyroidectomy because of recent growth in a long-standing mass on the left neck in a rural surgical clinic. Follicular thyroid carcinoma was diagnosed to display with widely invasive carcinoma (pT3N0) in pathology, so right near total thyroidectomy was conducted about one week later at the same clinic. The serum thyroglobulin was 38.53 ng/mL with TSH 0.3438 uIU/mL before surgery. When the patient was then referred to our hospital for further radioiodine therapy, the serum thyroglobulin had dropped to 1.58 ng/mL with TSH suppression (0.09 uIU/mL).

To evaluate the residual tumor burden, neck ultrasound was done three weeks after second surgery, which showed grouping lymphadenopathy with the largest diameter up to 1.79 centimeters at the left level V compartment. Lymph node metastases were suspected because of characteristic of malignant sonographic features with hyperechoic content, absence of hilum and hyper vascularity (Figure 1A). Aspirate cytology of the lymph nodes revealed a mixed population of lymphocytes and histiocytes. The lymph node aspirate for thyroglobulin measurement (LN-FNA-Tg) was undetectable (<0.16 ng/ml). Since lymph node metastasis could not be completely excluded, surgical intervention was conducted. The preoperative neck computed tomography (CT) also showed left level V grouping lymphadenopathy with perinodal infiltrations (Figure 1B). Left modified radical neck lymph node dissection

was performed, but excluded lymph node metastasis because of absent of any follicular cells. However, the dissected lymph nodes over the left III-V compartments demonstrated irregularly patchy necrotic lesions in paracortical areas (Figure 2A) with necrotic debris, fibrin deposit, and karyorhexis (nuclear debris). Surrounded by abundant histiocytes with pale cytoplasm, the center of the necrotic lesions was absent of any neutrophil infiltration (Figure 2B). Plasma cell infiltration was minimal except in the needle tract of the aspiration, which showed granulation tissue formation, edema and mixed inflammatory infiltration. The pathognomonic feature of SLE related lymphadenopathy, hematoxylin body, was not identified. Immunostaining with CD68 and myeloperoxidase disclosed numerous histiocytes within the lesions. The characteristic cytoplasmic granular staining pattern was identified in histiocytes (Figure 2C, D). These pathological findings were compatible with the characteristics of KFD. Reviewing the patient's history, she denied of any systemic disease and had no fever, malaise, or skin rash ever noted before or after the surgery.

Eventually, therapeutic ablation therapy with radioiodine 150mCi was carried out one and half months after lymph node dissection. The radioiodine whole body scan combined with single photon emission computed tomography (SPECT/CT) did not reveal any radioiodine avidity over the focal cervical lymph nodes but many small lymph nodes with interval shrinkage over level II, V, VI compartments, left supraclavical and upper cervical region still existed. Three months later, the patient remained afebrile and these above lymphadenopathies persisted in the follow-up neck ultrasound.

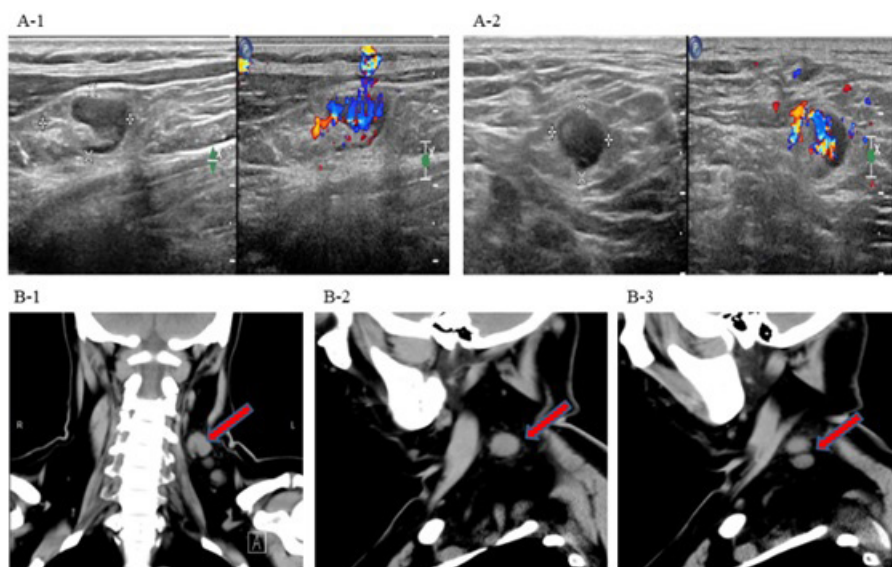


Figure 1: Lymph nodes detected by neck ultrasound (A) and computerized tomography (B). A1-2: The neck lymph nodes measured 1.79 cm in largest diameter were characterized by hyperechoic content, the absence of hilum and hypervascularity. B1-3: The neck lymph nodes (indicated by arrowhead) revealed perinodal infiltration over level V compartment

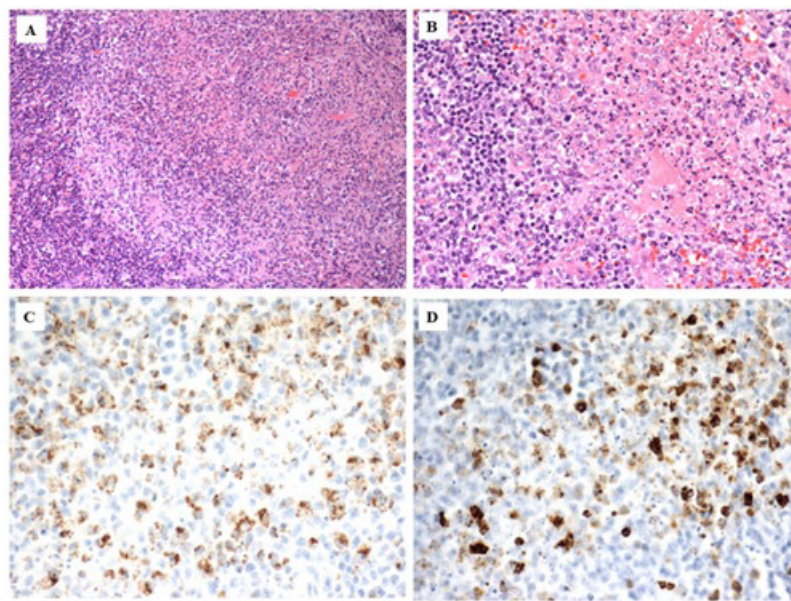


Figure 2: Histopathology of the Kikuchi-Fujimoto disease-related lymphadenopathy.

(A) Necrosis over the paracortical areas of the lymph node (40X); (B) Necrotic debris, fibrin deposit, and karyorhexis (nuclear debris) over center of the lymph node, absence of neutrophil infiltration (200X); (C) Infiltration of the monocytoid histiocytes in the periphery stained with CD68 (400X); (D) Infiltration of the monocytoid histiocytes in the periphery stained with myeloperoxidase (400X).

4. Discussion

The pathogenesis of the KFD is still unclear. An exaggerated immune response to infectious agents, such as various viruses and bacteria, has been hypothesized [1, 5, 6]. However, no definite evidence has ever been documented for the causal relationship [1]. Moreover, autoimmune-related exaggerated immune reaction has been mentioned because some cases of KFD coexisted with SLE or primary Sjögren's syndrome [5, 7]. These patients usually have more severe the KFD with extra-nodal manifestation and high fever [8]. The histopathologic features of the lymph node specimens share similar and clinical features in SLE and KFD. Therefore, clinical exclusion of SLE or primary Sjögren's syndrome should be done before definite diagnosis of KFD [4, 9]. Our case had no evidence of clinical symptoms and signs, and was negative for anti-dsDNA, antinuclear antibodies, normal C3 or C4 suggestive of SLE. Histopathological examination lacked follicular hyperplasia, no significant plasma cell population, and hematoxylin bodies, which all argued against the diagnosis of SLE.

Previously, a case of KFD was reported to occur after a breast implantation. The initial manifestation presented with a new breast lump with an irregular solid mass, angular margins, nonparallel orientation and hyper vascularity by breast ultrasound [10]. The lump was excised by core biopsy later and proved to be an intramammary lymph node of KFD. The sonographic features were similar to the characteristics of the neck lymphadenopathies with our current case. Jimenez-Heffernan et al. proposed that a local Kikuchi disease-like inflammatory reaction could be induced by the breast implant [11]. Perhaps, the KFD seen in our case could

have been caused by inflammatory reaction secondary to surgical manipulation and suturing after consecutive neck operations. This could be supported by evidence that no lymphadenopathies were detected at the time of thyroidectomy and the KFD occurred in this patient at a relatively older age.

Great variation exists in sonographic features of the affected lymph nodes in KFD. Some are hypoechoic with an external, thick and irregular hyperechoic ring, while some are characterized by an echogenic hilum with internal necrosis, normal hilar vascular pattern and absence of internal calcification [6, 12]. The characteristics of hyperechoic content and the absence of hilum in the lymph nodes in our case raised the suspicion of lymph node metastasis of thyroid cancer [13]. LN-FNA-Tg may be a reliable diagnostic method in distinguishing between KFD and lymph node metastasis from differentiated thyroid cancer. A LN-FNA-Tg level higher than 10 ng/ml strongly favors lymph node metastasis [14]. The negative cytology and undetectable level of LN-FNA-Tg in our case also supports the clinical significance of this diagnostic method.

Even though lymph node metastasis is less common (2-8%) in patients with follicular thyroid carcinoma, it is seen in up to 17% of cases of widely invasive follicular thyroid carcinoma [15-17]. KFD coexisting with micro medullary carcinoma or follicular adenoma is quite unusual and there are only few reports [18, 19]. KFD mimicking lymph node metastasis in patients with prior thyroid cancer has likewise only been reported in a few cases [20-22]. But differential diagnosis of the lymph node metastasis versus KFD is still limited when examined by neck ultrasound, CT scan or pos-

itron emission tomography (PET) scan [23]. Since the sensitivity and specificity of neck ultrasound to detect lymph node metastasis is not good enough, LN-FNA-Tg combined with lymph node aspirate cytology may offer an accurate way to distinguish lymph node metastasis from differentiated thyroid cancers [13, 14]. We proposed that LN-FNA-Tg combined with lymph node aspirate cytology may be useful to differentiate lymph node metastasis from thyroid cancer with other etiologies. And it could avoid unnecessary surgical intervention.

The principal mechanism of KFD-associated cellular destruction is apoptotic cell death, mediated by cytotoxic T lymphocytes and enhanced by histiocytes. The majority of cells in the necrotic lesions were CD8+, CD3+ T-lymphocytes and CD68+ histiocytes with very few B-lymphocytes [9, 24]. The apoptotic cells show characteristic of condensation and fragmentation of nuclear chromatin and phagocytosing karyorrhectic debris (apoptotic bodies) of histiocytes by microscopy [1, 5, 9]. In our case, the lymph node aspirate showing abundant of karyorrhectic debris and histiocytes but absent cohesive epithelial cell clusters was strongly indicative of KFD. Immunocytochemical studies of epithelial markers (AE1/AE3 and CAM5.2), histiocytic markers (CD68 and myeloperoxidase), and thyroid epithelial markers (TTF-1 and PAX-8) have also been reported beneficial for differential diagnosis [25].

KFD is usually a self-limited benign disease and resolves within one to six months. Fatality is extremely rare except secondary to lymphoproliferative disease or complicated with neurologic manifestations [26]. According to a retrospective study of 91 cases with KFD, 61.5% of the patients recovered spontaneously without treatment [7]. Supportive treatment with antipyretics and analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) is the primary approach for symptom relief. Steroids (prednisolone 0.5–1 mg/kg) are the mainstay of treatment for more severe cases [1, 27]. Some immunosuppressive agents (hydroxychloroquine, cyclosporine, and azathioprine) and immunoglobulin are also reported to have benefits in some patients [28, 29].

5. Conclusion

In conclusion, thyroid cancer simultaneous with KFD is extremely rare. However, it should be considered and differentiated further in patients with follicular thyroid carcinoma concurrent with lymphadenopathy. Early recognition of KFD is critical to minimize potentially harmful and unnecessary examinations and treatments. To avoid unnecessary surgical intervention, use of lymph node aspirate cytology combined with LN-FNA-Tg could offer valuable information to exclude lymph node metastasis.

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