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Type 2 Diabetes Mellitus with Primary Myelofibrosis and Hashimoto's Thyroiditis: A Case Report

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Abstract

This report described a case of primary myelofibrosis patient, who has a medical history of 20 years type 2 diabetes mellitus and 4-year Hashimoto's thyroiditis. The patient was admitted to our hospital due to lower limbs edema, and then developed dyspnea while walking. Physical examination revealed exuberant peripheral edema and jugular venous distention. Magnetic resonance imaging scan showed enlarged spleen. Blood tests showed an elevated white blood cells, LDH, and natriuretic peptide. Bone marrow biopsy reveled megakaryocytic hyperplasia and atypia, fibroblast proliferation and increased bone trabecula. Gene tests detected JAK2V617F mutation, without the BCR-ABL. These clinical and laboratory evidences support the diagnosis of Primary Myelofibrosis. Following 2 months treatment of hydroxyurea, danazol, thalidomide, and ruxolitinib, the clinical symptoms and physical signs were improved, but anemia progressed and suggested high risk patient.

Chronic inflammation, insulin resistance, hyperinsulinemia, and insulin treatments of type 2 diabetes mellitus, and potentially Hashimoto's thyroiditis, may be associated with developmental primary myelofibrosis.

Introduction

Type 2 Diabetes Mellitus (T2DM) is an endocrine metabolic disorder with a rapid increasing prevalence, which is characterized by high blood glucose concentration due to insufficient to secretion of pancreatic insulin and insulin activity or altogether [1]. Hashimoto's Thyroiditis (HT) is a condition of chronic lymphocytic thyroiditis. HT is characterized by an inflammatory infiltrate of lymphocytes that replace the parenchyma and subsequently resulting in impaired thyroid hormone production and clinical hypothyroidism [2]. Primary Myelofibrosis (PMF) is a Myeloproliferative Neoplasms (MPN) characterized by megakaryocyte proliferation and atypia, leukoerythroblastosis and bone marrow fibrosis [3]. Clonal abnormality, for example JAK2V617F, MPL, TET2, in pluripotential stem cells causes BCR-ABL1-negative MPN [4]. The main clinical manifestations are anemia, splenomegaly, fever, and progressive debilitation leading cachexia [5]. T2DM and HT share the pathology of inflammation, which is that insulin resistance would result in the activation of some proinflammatory factors, meanwhile, chronic inflammatory can cause insulin resistance and HT [6-8]. Some studies found T2DM increase the cancer risk, including the blood cancer, partially owing to hyperinsulinemia. Insulin can activate the functional receptor of Insulin-like Growth Factor (IGF-1) leading to activating the downstream signaling pathways leading to unregulated IGF-1 function [9]. Over expression of IGFs can lead to abnormal proliferation and differentiation of cell [10].

We report a patient with T2FM who developed HT, then PMF. The discussion of potential biological links of these conditions, if any may provide the sign in early diagnosis and effective management of T2DM to prevent the cancer [11,12].

Case Presentation

The patient is a female, 70 years old, with a history of 20 years T2DM and insulin-dependent therapy. The patient was also diagnosed as HT for 4 years and received levothyroxine therapy. The patient has started to experience mild edema in her lower limbs from March 2018. Blood test showed an elevated White Blood Cell (WBC) count of 13.69 × 10^9/L (Normal Range [NR]: 3.5 to 9.5). An abdominal ultrasound reveled splenomegaly. WBC count remained to be high of 13.42 × 10^9/L two months later with an increase of Brain Natriuretic Peptide (BNP) (183.28 pg/mL [NR:

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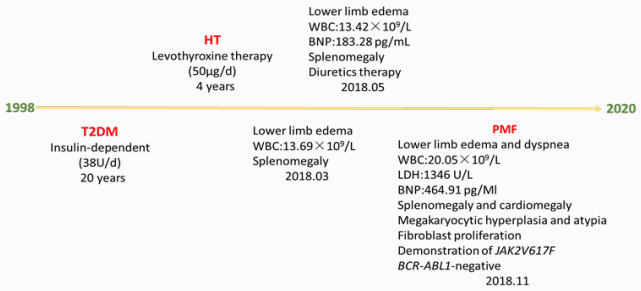

Figure 1: The time line of the patient's medical history.
T2DM: Type 2 Diabetes Mellitus; HT: Hashimoto's Thyroiditis; PMF: Primary Myelofibrosis; WBC: White Blood Cell; BNP: Brain Natriuretic Peptide; LDH: Lactic Dehydrogenase

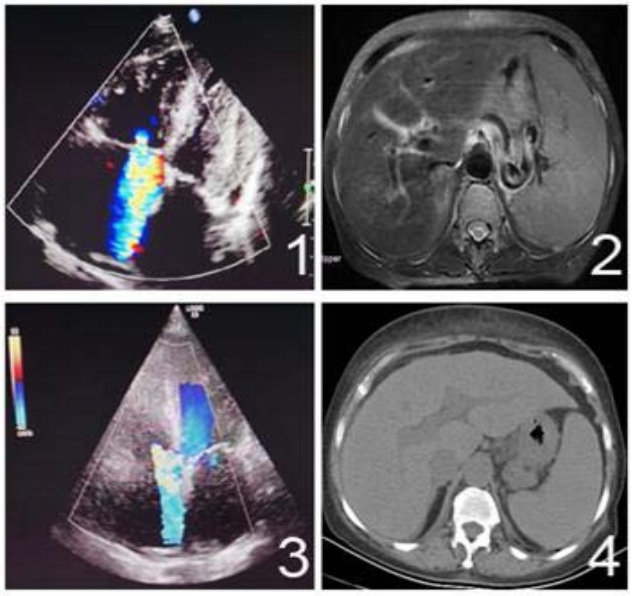

Figure 2: The images show the Doppler echocardiography and splenic radiography before (1, 2) and after (3, 4) treatments. (1) Before treatment, cardiac ultrasound showing right ventricular enlarge (4.9 cm [NR: 3.2-4.4]), and the quantity tricuspid regurgitation and speed is 4.7 m/s. (2) Before treatment, abdomen MRI showing the severe splenomegaly. (3) After treatment, cardiac ultrasound showing right ventricular enlarge (4.4 cm [NR: 3.2-4.4]), and the quantity tricuspid regurgitation and the speed is 3.7 m/s. (4) After treatment, abdomen MRI showing the mild splenomegaly.

0 to 100]), Alkaline Phosphatase (ALP) (153 U/L [NR: 50 to 135]). A cardiac ultrasound was normal. A Computed Tomography (CT) scan showed a persistent splenomegaly. The edema was reduced after 5 days treatment of diuretics. The patient was discharged. The time line of her medical history is shown in (Figure 1).

T2DM, type 2 diabetes mellitus, HT, Hashimoto's thyroiditis, PMF, Primary myelofibrosis, WBC, white blood cell, BNP, brain natriuretic peptide, LDH, Lactic dehydrogenase.

In December 2018, she started to complain for progressive dyspnea during shorter and lower limb edema. Physical examinations found exuberant peripheral edema, jugular venous distention and enlarged spleen. Cardiac ultrasound showed cardiomegaly (Figure 2.1). Abdominal Magnetic Resonance Imaging (MRI) scan showed enlarged spleen (Figure 2.2).

Laboratory test demonstrated the elevated aspartate aminotransferase (54 U/L [NR: 0 to 40]), alkaline phosphatase (202

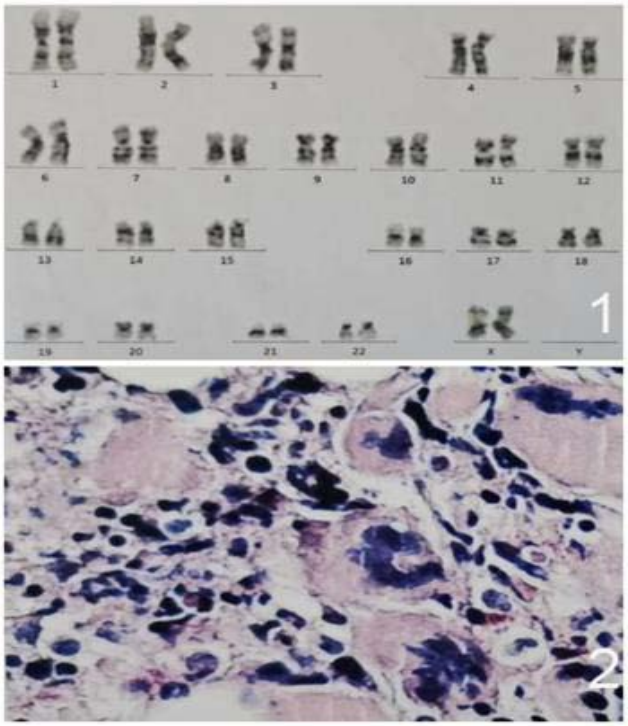

Figure 3: (1) Karyotype showing 46, XX, and normal. (2) Bone marrow biopsy showing megakaryocytic hyperplasia and atypia, fibroblast proliferation, and increased bone trabecula.

U/L [NR: 8 to 57]), and gamma-glutamyl transferase (178 U/L [NR: 30 to 120]) with normal Red Blood Cell (RBC) count of 4.73×10^{12}/L (NR: 3.8 to 5.1), the Platelet (PLT) count of 244×10^{9}/L (NR: 125 to 350). WBC (20.05×10^{9}/L [NR: 3.5 to 9.5]), neutrophil (NE 15.49×10^{9}/L [NR: 1.8 to 6.3]), lactic dehydrogenase (1346 U/L [NR: 100 to 250]), and brain natriuretic peptide (464.91 pg/ml [NR: 0 to 100]) were very high, and albumin (28.5 g/L [NR: 40 to 55]) and hemoglobin (HGB 104 g/L [NR: 115 to 150]) were low.

A peripheral blood smear showed an increased segmented granulocyte and age-adjusted erythrocyte. The immunohistochemical analysis showed a mild higher ratio 1.1% for CD34+ bone marrow blasts in nucleated cell, with normal phenotype, and an abnormal pattern of granulocytes development. The karyotype was 46, XX, and remain normal (Figure 3.1). The *JAK2V617F* mutation was detected; however the qualitative polymerase chain reaction was negative for the BCR-ABL fusion transcript. A bone marrow biopsy showed megakaryocytic hyperplasia and atypia, fibroblast proliferation and increased bone trabecula (Figure 3.2). The patient was diagnosed as PMF, after excluding other myeloid disorders, vascular, infections, and autoimmune cause.

The patient had been treated for anemia and symptomatic splenomegaly with hydroxyurea (0.5 g/d), danazol (600 mg/d), thalidomide (100 mg/d), and ruxolitinib (10 mg/d). After 2 months treatment, the lower limb edema was reduced, and cardiac ultrasound and abdomen CT showed shrunken cardiomegaly and splenomegaly (Figure 2.3 and 2.4). Blood analysis showed the decrease of WBC (7.68×10^{9}/L), RBC (3.8×10^{12}/L) and HGB (89 g/L) (Table 1). The treatment was then adjusted to stop using hydroxyurea and thalidomide, and continue to use ruxolitinib (10 mg/d) and danazol (200 mg/d).

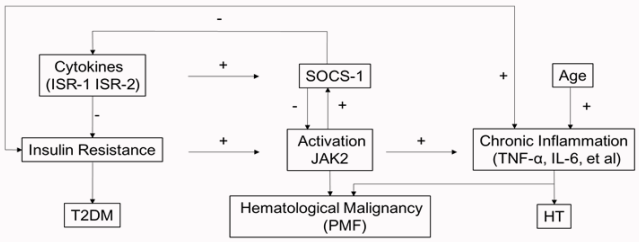

Figure 4: The possible link between T2DM, HT and PMF.
T2DM: Type 2 Diabetes Mellitus; HT: Hashimoto's Thyroiditis; PMF: Primary Myelofibrosis; JAK2: Janus Kinase 2; ISR: Insulin Receptor Substrates; SOCS-1: The Suppressors of Cytokine Signaling-1
+: Activation
-: Inhibition

Table 1: The blood cells counts and HGB level of the patient.

	Time	WBC ($\times10^9$/L)	RBC ($\times10^{12}$/L)	HGB (g/L)	PLT ($\times10^9$/L)
Before treatment	2018.03	13.69	4.67	115	230
	2018.05	13.42	4.31	101	250
	2018.11	20.05	4.73	104	244
After treatment	2019.01	7.68	3.8	89	317
	2019.05	10.27	1.9	57	231
	2019.12	9.05	2.52	81	448

WBC: White Blood Cell; RBC: Red Blood Cell; HGB: Hemoglobin; PLT: Platelet

The patient had once 2 U red blood cell transfusion since May 2019 because of severe anemia (Table 1).

Discussion

Primary myelofibrosis is approximately 65% mutation ratio of *JAK2V617F*, activate by *JAK2* gene mutation of overexpression [13]. T2DM has been reported to be associated with the overexpression of cytokine signaling-1 (SCOS-1) leading to degrade the Insulin Receptor Substrates (ISR-1 and ISR-2) [14]. The overexpression of SCOS-1 activates Janus kinase 2 (JAK2) and the Signal Transducer and Activator of Transcription 3 (STAT3) result in insulin resistance and inflammation [15]. There is a negative feedback loop between SOCS-1 and *JAK2/STAT3* [16]. The chronic inflammation is implicated in the pathogenesis of Hashimoto's thyroiditis [17]. Also, chronic inflammation is characterized by a mild elevation of pro-inflammation, including Tumor Necrosis Factor (TNF-α) and Interleulin-6 (IL-6) and so on, which has been associated with insulin resistance, diabetes, HT and second cancer [18,19]. Our interpretation is that there may be a link between T2DM, HT and PMF, as shown in the picture (Figure 4), but we are not sure.

High concentration of insulin in T2DM due to insulin resistance and insulin treatment has been suggested to link to cancer including myelofibrosis [20]. IGF-1 and IGF-2 are the growth factors. The mitogen effects of IGFs have been suggested through promoting abnormal cell proliferation and migration through activating IGF-1 receptor [21]. In 2004, Bock et al. [22] reported that IGF-2 overexpression had been observed in idiopathic myelofibrosis. Even through insulin has a lower affinity to IGF-1 receptors; an elevated insulin concentration in plasma can activate the downstream signaling pathway and inhibiting physiological apoptosis [23]. Twenty years of insulin replacement therapy and insulin resistance may contribute to the development of PMF. Unfortunately, we didn't have control born marrow samples to allow us to determine whether there is elevated IGF-1receptor phosphorylation.

The patient remained to be cardiac manifestations of PMF and lower limb edema, with slightly elevated WBC count and no anemia. The non-classical clinic manifestation leads to the delayed diagnosis and treatment, given that the diagnosis of PMF is based on the exclusion of other myeloid disorders, vascular disease, infection disease, or autoimmunopathy. Laboratory and iconography, bone marrow biopsy and cytogenetic studies may assist early diagnosis, but differential diagnosis remains difficult.

The initial symptoms of mild elevation of WBC count milled the investigation which did not take hematological diseases into account. Because, we failed to see that leukocytosis coexist with splenomegaly. The treatment for PMF, improved the cardiomegaly (Figure 2.3) and splenomegaly (Figure 2.4), and other clinical manifestations, excepting the anemia owing to the patient refuse allogeneic stem-cell transplantation.

Heart failure accompanied by mild leukocytosis and splenomegaly could be considered as a rare initial manifestation of PMF in patient with T2DM and HT, to early diagnosis and treatment.

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