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CASE REPORT

A Rare Association of Mauriac Syndrome and Van Wyk–Grumbach Syndrome Found in a Young Saudi Girl: A Case Report and Brief Literature Review

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by insufficient insulin production of the pancreatic beta-cells. Patients with T1DM will have a higher risk of other autoimmune disorders like celiac and thyroid diseases. Hypothyroidism is the failure of the thyroid gland to secrete an adequate amount of thyroxine, which is required for physical growth, brain development, and cellular metabolism. Most studies reported that children with T1DM have a higher incidence of hypothyroidism than normal children, with 9.6% having hypothyroidism and 19% having positive anti-TPO antibodies. Hypothyroidism will aggravate the condition in a child with T1DM and vice versa. Uncontrolled diabetes for a long time might increase insulin resistance due to complete depression of the hypothalamus-pituitary thyroid axis. A rare complication of poorly controlled T1DM is Mauriac syndrome, characterized by elevated liver enzymes, hyperlipidemia, cushingoid features, growth retardation, and hepatomegaly due to glycogenic hepatopathy. Van Wyk–Grumbach syndrome is also a rare complication of long-standing, untreated hypothyroidism, manifested by breast development, multicystic ovary, uterine bleeding associated with lack of pubic and axillary hair growth, and delayed bone age. Here, we report a case with two rare complications of Mauriac syndrome and Van Wyk–Grumbach syndrome in a child with hypothyroidism and poorly controlled T1DM.

KEYWORDS: Type 1 Diabetes, Hashimoto Thyroiditis, Mauriac Syndrome, Van Wyk–Grumbach Syndrome, Diabetes Complications

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by insufficient insulin production of the pancreatic beta-cells. Patients with this disease are more likely to develop other autoimmune disorders, such as celiac disease and thyroid disease [1]. Hypothyroidism is the failure of the thyroid gland to secrete an adequate amount of thyroxine, which has an essential role in physical growth, brain development, and cellular metabolism [2]. In 2017, Fatourechi A. et al. found that children with T1DM have a higher incidence of hypothyroidism than normal children, with a hypothyroidism incidence rate of 9.6% and 19% having positive anti-TPO antibodies [3]. Moreover, the consanguinity rate is higher among parents of children with T1DM and hypothyroidism than that of children with T1DM who had normal thyroid function and with a higher rate of diabetes mellitus in their first-degree relatives. Also, they had significantly higher rates of diabetic ketoacidosis (DKA) at initial diagnosis and required higher insulin doses to control their disease. Hypothyroidism will aggravate the condition in a child with T1DM and vice versa. The thyroid hormone enhances glucose uptake into peripheral tissue and has an additive effect on insulin action. Uncontrolled diabetes for a long time might increase insulin resistance due to complete depression of the hypothalamus-pituitary-thyroid axis [3]. In two studies, the researchers found that impaired thyroid function was associated with a severe metabolic imbalance in patients with newly diagnosed T1DM and observed significantly lower levels of thyroid hormones in newly diagnosed T1DM children who presented with DKA than those in patients without DKA at initial diagnosis. A rare complication of poorly controlled T1DM is Mauriac syndrome, characterized by elevated liver enzymes,

hyperlipidemia, cushingoid features, growth retardation, and hepatomegaly due to glycogenic hepatopathy [4]. Van Wyk–Grumbach syndrome is also a rare complication of long-standing, untreated hypothyroidism, manifested by breast development, multicystic ovary, uterine bleeding associated with lack of pubic and axillary hair growth, and delayed bone age [5]. Here, we report a case with two rare complications of Mauriac syndrome and Van Wyk–Grumbach syndrome in a child with hypothyroidism and poorly controlled T1DM.

CASE REPORT

An 11-year-old female was diagnosed with T1DM at the age of 9 months. Since that time, her diabetes has remained uncontrolled with frequent visits to the endocrine clinic every three to four months with poor compliance to medication and lack of laboratory investigation. At the age of 4, she was diagnosed with Hashimoto thyroiditis with a high thyroid-stimulating hormone (TSH) level of 23.6 mIU/L, FT4 of 10 pmol/L, and positive thyroid peroxidase antibodies (TPO). She has been taking levothyroxine since that time. In 2017, we noticed that the patient was not growing well on the growth chart and had lipohypertrophy in all limbs with no other abnormal findings. The patient and her mother were informed and educated on the condition. And at the age of 11, her breasts increased in size, and the Tanner stage was III without other signs of puberty. She had frequent admission to our hospital due to DKA. Upon physical examination during the last admission, the patient had a cushingoid face with a depressed nasal bridge and a prominent forehead, significantly short, with a Z score of 3.82. Tanner's stages involve breast stage IV without pubic hair, and her thyroid gland was not palpable. Abdominal examination revealed hepatomegaly, and the liver span was 15 cm (8 cm below the costal margin). Lipohypertrophy over all limbs was recognized. Thus, we question the complication of hypothyroidism and T1DM, so investigations were conducted to understand the rare complication of both diseases. The investigation showed an abnormal thyroid panel with a very high TSH level reaching 392.66 mIU/L and a low free T4 of 5.2 pmol/L, Hg□1C was 15%, celiac antibodies were negative, and ACTH, cortisol level, and insulin-like growth factor were within normal limit. Her bone age study showed delayed bone age of nine years (Figure 1), and mild anterior pituitary enlargement with a convex upper margin was confirmed using a pituitary fossa MRI (Figure 2). The pelvic ultrasound saw several small follicles in both ovaries (Figure 3). Abdomen ultrasound confirmed hepatomegaly (16.1 cm). Although the liver transaminase level was normal, the liver biopsy showed minimal focal nflammation in the portal tract with minimal glycogen deposition (Figure 4).

DISCUSSION

Mauriac described the Mauriac syndrome in 1930 as hepatic glycogenosis in diabetic children with cushingoid facial features, poor growth, and hyperlipidemia. However, hepatic glycogenosis without another hallmark of the syndrome was reported [6]. Mauriac syndrome can occur in children and adults and is a complication of neonatal diabetes mellitus, poorly controlled T1DM, and rarely T2DM [4]. Patients with Mauriac syndrome may present with clinical signs of DKA, such as abdominal pain and vomiting, as in the case of our patient, or they are asymptomatic with elevated liver enzymes and hepatomegaly [6]. Other presentations of this syndrome are signs of acute hepatitis, jaundice, pruritus, and elevated plasma lactate levels with or without DKA, as mentioned in a few reports [4]. Our patient had the usual clinical presentation, including hepatomegaly, growth failure, and cushingoid facial feature [4]. Hyperglycemia and hyperinsulinemia are two components in the pathophysiologic process of glycogenic hepatopathy [6].

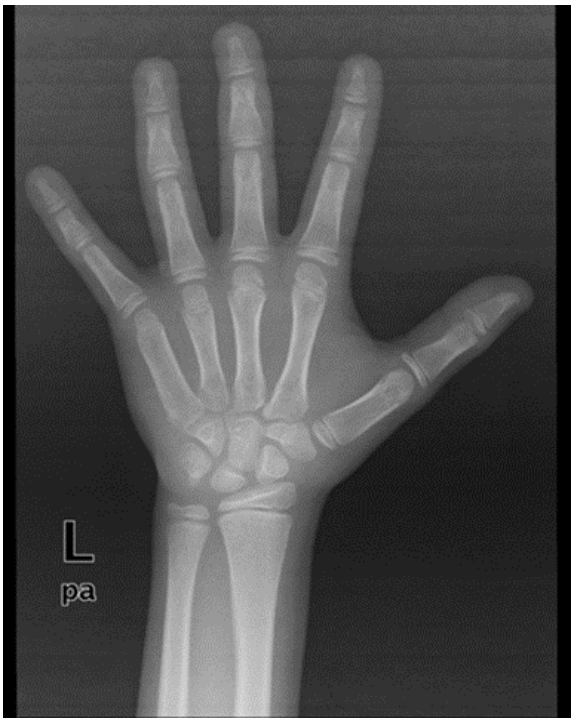

Figure 1: Using Greulich and Pyle atlas; approximate bone age is about 8 years

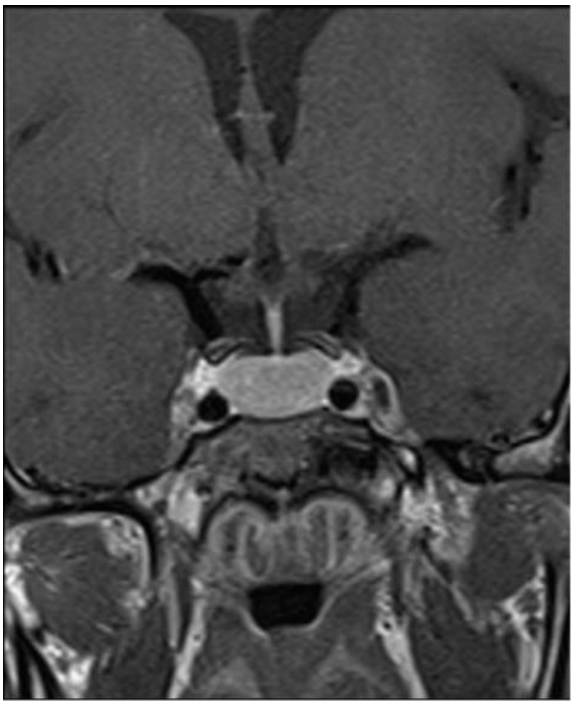

Figure 2: Mildly enlarged anterior pituitary with convex upper margin.

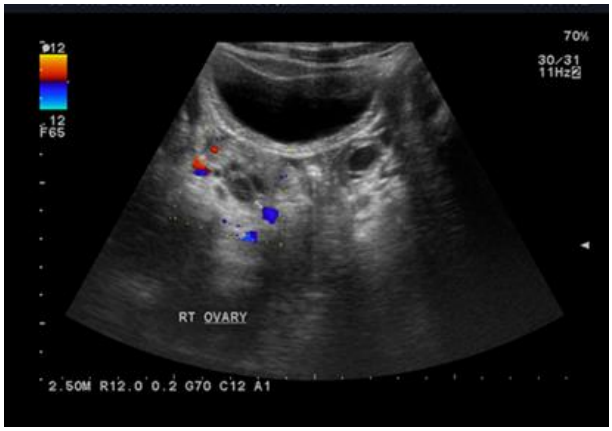

Figure 3: Right ovary measures 2.3 x 1.4 x 1.6 cm with an average volume of 2.8 ml and left ovary measures 2.6 x 1.5 x 2.0 cm with an average volume of 4.1 ml. Multiple small follicles are seen in both ovaries.

Passive diffusion leads to an influx of glucose into the hepatocytes in hyperglycemia, then irreversibly converting glucose to glucose 6-phosphate [4]. Hyperglycemia increases the need for insulin in a patient with poorly controlled T1DM, and a higher amount of insulin administration leads to the activation of glycogen synthase, which promotes hepatic glycogen storage [6]. Several authors described this vicious cycle as the primary mechanism of the excessive accumulation of glycogen in hepatocytes that rapidly lead to liver injury [4]. The fluctuation in the blood glucose level leads to secondary hyperadrenalism that causes cushingoid features in the classic presentation of Mauriac syndrome [4]. Releasing excessive cortisol could result in delayed growth and puberty and decreased circulating insulin-like growth factor-1 (IGF-1) with a relatively resistant state of growth hormone [4]. On the other hand, corticosteroid use and poorly controlled T1DM and T2DM are the most well-known causes of acquired glycogenic hepatopathy [4,6]

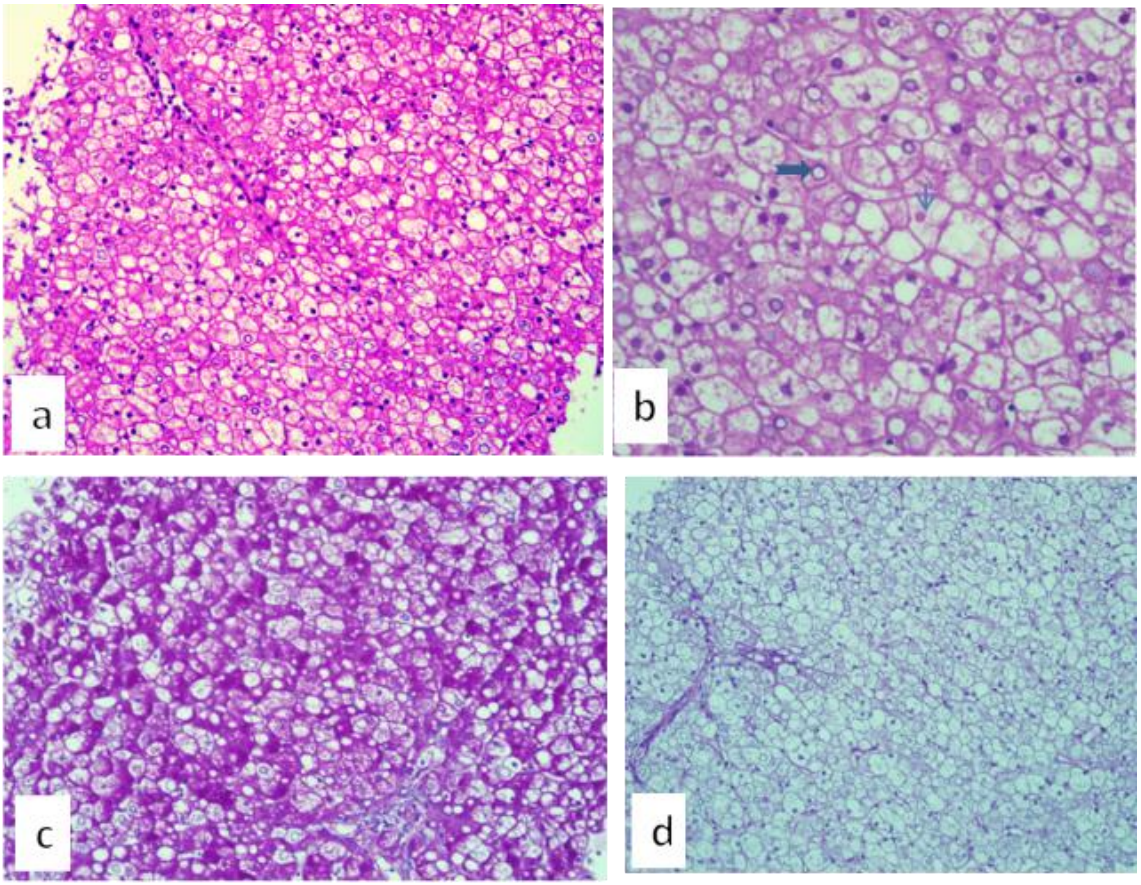

Figure 4: a +b- HE staining x 200, HE staining x 400: the hepatocytes are swollen with pale or eosinophilic cytoplasm and accentuation of the cell membranes. The sinusoids are compressed. Glycogenated nuclei (notched arrow) and megamitochondria (arrow) are identified. c+d: PAS staining, PAS staining with digestion by diastase, showed glycogen accumulation in the hepatocytes

Some reports revealed other reasons for glycogen hepatopathy, including a toddler with dumping syndrome associated with gastrostomy feeding without glucose intolerance, a 15-year-old boy with a well-controlled T2DM, and three children treated by high-dose glucocorticoid without DM [7]. Moreover, the development of Mauriac syndrome is associated with some genetic mutations, such as KCNJ11 mutation, INS mutation, and PHKG2 mutation, that cause prolonged permanent neonatal diabetes [4]. The differential diagnosis of a patient with T1DM with hepatomegaly or elevated serum liver enzymes should include the classic causes of liver damage and hepatomegaly, like nonalcoholic steatohepatitis (NASH) and congenital glycogen storage diseases. NASH is characterized by cirrhosis and weight loss. On the other hand, hereditary glycogen storage disease causes hypoglycemic episodes, hepatomegaly, lactic acidosis, growth retardation, and hyperlipidemia, with hepatic glycogenosis [6]. Other differential diagnoses are acute, chronic, or autoimmune hepatitis [4]. We performed several tests on our patient to confirm the diagnosis, including serology and liver biopsy, which are

the gold standard for distinguishing Mauriac syndrome from other causes of hepatomegaly, such as nonalcoholic fatty liver disease (NAFLD), which cannot be distinguished entirely either clinically or radiologically by ultrasound (US) or even computed tomography (CT) [4,7]. Torbenson et al. showed that liver transaminase levels could be dramatically elevated, up to 10 times above normal, in patients with glycogenic hepatopathy with preserved liver synthetic function [6]. Because our patient has normal liver transaminase, other differential diagnoses were excluded, including hepatocellular and cholestatic injury [7]. Histopathological glycogenic hepatopathy (GH) characteristics include swollen hepatocytes caused by glycogen accumulation without or with mild fatty change, minimal inflammation, minimal spotty lobular necrosis, and intact architecture without significant fibrosis. Mild steatosis may be present or absent, and the hallmark of this condition is glycogen accumulation [7]. As previously stated, Mauriac syndrome does not typically exhibit significant fibrosis, but focal portal fibrosis and bridging fibrosis have been reported in some cases, which is an unusual finding, and the exact mechanism responsible for fibrosis development remains unclear [4]. All the clinical features of Mauriac syndrome, including growth failure, hepatomegaly, and glycogen deposition, return to normal with optimal insulin therapy and strict blood glucose levels. Regression of Mauriac features differs according to the patient: some take two weeks to be normalized, and others take four weeks; however, if hepatomegaly persists for more than four weeks, other causes should be ruled out [6]. One case report showed that after four months of changing the insulin treatment regimen, GH appeared and then resolved rapidly after extensive insulin therapy [7]. Indication of pancreatic transplantation in a patient with T1DM has been found to reduce diabetic complications by improving glycemic control in patients with Mauriac syndrome [6]. End-stage liver damage, synthetic dysfunction, hepatocellular carcinoma, or portal hypertension are fatal complications of GH itself and, fortunately, have never been reported [7]. In patients with Mauriac syndrome, deterioration of retinopathy and nephropathy were caused by aggressive insulin treatment, so patient education is essential in all diabetic patients to minimize complications and reverse the clinical features of Mauriac syndrome by optimal insulin therapy [6]. Unfortunately, our patient has another autoimmune disease, which is Hashimoto thyroiditis, which is considered the most frequent cause of acquired thyroid disorder during childhood and adolescence. Hashimoto thyroiditis is characterized by the production of thyroid autoantibodies, such as anti-TPO, thyroglobulin (anti-TG), and thyroid-stimulating hormone receptors (TSHRs), through T and B lymphocytes infiltration to the thyroid and reaction against thyroid antigens, leading to fibrous replacement and parenchymal atrophy. The disease outcome is affected by existential/environmental factors and genetic background. The patient has hypothyroidism due to clinical and biochemical alterations that result from autoimmune gland injury [8-10]. The prevalent disease among children with diabetes is hypothyroidism, associated with higher DKA rates and requiring higher insulin doses, and both diseases share common genetic factors and immunologic processes [1,3]. Our patient has the hallmark of Van Wyk–Grumbach syndrome, which includes isosexual precocious puberty resulting from long-standing untreated hypothyroidism [11]. Van Wyk and Grumbach described this syndrome for the first time in 1960, and clinical features of girls with this syndrome include breast development, follicular cysts visible in the histopathological analysis of resected ovaries and ovarian cysts, and menstruation with no pubic or axillary hair [12]. Some reports noted myxoedematous infiltration within the affected ovaries, implying an independent role in cyst formation and abnormal steroidogenesis in the gonad. Van Wyk–Grumbach syndrome can occur in boys characterized by macroorchidism without significant virilization. The predominance of tubular elements without elevated Leydig cell numbers in testicular histology was consistent with an FSH-mediated response. In early development, thyroid hormone is known to affect the growth and physiology of the testis, while in Van Wyk–Grumbach syndrome, the function of thyroid hormone receptors on Sertoli and Leydig cells is currently poorly understood [12]. These symptoms occur due to the elevation of thyroid-releasing hormone caused by the lack of negative feedback on the pituitary from the thyroid hormone deficiency resulting in an overlap in pituitary hormone secretion [13]. The glycoprotein of TSH shares a common alpha-subunit with follicle-stimulating hormone (FSH), luteinizing hormone (LH), and human chorionic gonadotropin (hCG). Still, each hormone has a unique beta-subunit. Each hormone stimulates cAMP production through adenylate cyclase activation by transmembrane GPCRs. Anasti et al. showed that recombinant human TSH elicited a dose-dependent response at the human FSH receptor. The FSH-like activity of TSH is deficient because the requirement of TSH concentration was several orders of magnitude higher than FSH. The TSH competitively antagonizes FSH because both TSH and FSH are acting on the same receptor. Still, not all glycoproteins have the same response; for example, hCG was unresponsive to adenylate cyclase activity in transfected cells [12]. Thus, the development of secondary sexual characters results from increased estrogen production due to the elevation of TSH on the FSH receptor. Furthermore, the absence of pubic and axillary hair results from the unaffected adrenal gland and normal hormones. Another explanation for isosexual precocious puberty is hyperprolactinemia caused by pituitary thyrotrophic hyperplasia, which compresses the pituitary stalk and disrupts hypothalamic inhibition of prolactin, or by direct stimulation of prolactin release by thyrotropin-releasing hormone (TRH) [5]. Pituitary gonadotropins suppressed by prolactin through slowing gonadotropin-releasing hormone (GnRH) pulse frequency cause FSH production and suppression of LH [12]. In our case, an MRI of the pituitary gland showed mild anterior pituitary enlargement due to the lack of negative feedback on the pituitary [5]. A patient with this syndrome may also present with skin hyperpigmentation due to hormonal overlapping with the melanocyte-stimulating hormone (MSH) that acts on G protein-coupled receptor (GPCR) [12]. Association of Trisomy 21 or Kocher-Debre-Semelaigne syndrome with this syndrome have been reported in various atypical cases of Van Wyk–Grumbach syndrome; moreover, the patient can present with unilateral ovarian mass or has a presentation of this syndrome in adulthood [5]. Elevated tumor markers can present in some patients with VWGS, like CA-125 and alpha-fetoprotein (AFP). Both are nonspecific and related to other conditions, such as endometriosis, uterine fibroids, tubo-ovarian mass, dysgerminomas, and other germ cell tumors. Replacement of thyroid hormone has been found to normalize AFP; thus, the tumor marker elevation occurs secondary to ovarian hyperstimulation and cyst formation, not due to cancer [14]. Bone age is determined by various methods, such as the appearance of epiphysis in X-rays of the wrist and hand that determine linear growth and

comparing the patient's ossification centers with published age-matched standards derived from healthy children using the Greulich and Pyle atlas [5]. Most precocious puberty causes are associated with advanced bone age; thus, delayed bone age is a unique diagnostic clue for VWGS [14]. VWGS can be manifested as hypertrichosis in long-standing untreated hypothyroidism associated with accelerated precocious puberty and delayed bone age, while in all other causes of precocious puberty, bone age will be advanced [15]. Van Wyk–Grumbach syndrome can be found in other causes of hypothyroidism, such as congenital hypothyroidism, ectopic thyroid tissue, or hypothyroidism tumors [16]. As in Mauriac syndrome, early recognition of the Van Wyk–Grumbach syndrome and initiation of thyroid hormone replacement reverse all the symptoms with normalization of hormonal profile through negative feedback on pituitary hyperplasia, and the patient will regain growth velocity resumption [5,13,14]. Furthermore, patients with dysfunctional uterine bleeding may need estrogen treatment in the short term. Therefore, any exogenous estrogen should be discontinued after normalization of TSH levels to optimize final adult height [13]. According to several authors, surgical interventions, such as ovarian cystectomy or oophorectomy, should reverse the condition for patients with torsion, ovarian rupture, hemodynamic instability, or failure to regress with thyroid hormone replacement [14]. Other consequences of prolonged untreated hypothyroidism include macrocytic anemia due to suppression of bone marrow with erythropoietin secretion and pericardial effusion through increased capillary permeability, leading to extravasation of the pericardial sac by protein-rich fluid that increased salt and water retention and impaired lymphatic drainage [17].

CONCLUSION

Our case is peculiar because of the rare association of the Mauriac syndrome with the Van Wyk–Grumbach syndrome in the same patient with hypothyroidism and poorly controlled DM type 1. Patient education and medication compliance are essential in all patients with diabetes associated with hypothyroidism to reduce complications and reverse the clinical features of the Mauriac syndrome with Van Wyk–Grumbach syndrome.

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AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship, and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors.

COMPETING INTERESTS

The author declares no competing interests in this case.

PATIENT'S CONSENT

Written informed consent was obtained from the patient for the publication of this case report.

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