Persistent Hypothyroidism Despite Standard Levothyroxine Treatment: A Case Study of Tissue Hypothyroidism

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ABSTRACT

Despite hormone replacement therapy with levothyroxine sodium, some patients continue to complain of overt signs and symptoms of hypothyroidism, despite having normal labs. In some cases, there is no identifiable correlation with comorbidity and/or medication interfering with an optimal response; tissue hypothyroidism may be the reason for the observed signs and symptoms in these patients. We report a case of a 54-year-old Afro-Caribbean female who has been diagnosed with hypothyroidism for the past 26 years but was started on hormone replacement therapy with levothyroxine after bilateral partial lobectomy 19 years ago. The patient is currently on the standard levothyroxine therapy in tablet form, yet for the past 16 years has been complaining of persistent signs and symptoms of hypothyroidism; fatigue, dry skin, brittle hair and nails, cold intolerance, constipation, and unintentional weight gain. Normal laboratory findings and thyroid function tests confirm that the patient is given optimal doses of treatment. This case may suggest the presence of tissue resistance to levothyroxine, resulting in the persistence of signs and symptoms of hypothyroidism.

Key words: Euthyroidism, hypothyroidism, levothyroxine sodium, selenium

BACKGROUND

The standard treatment of hypothyroidism is levothyroxine sodium; however, despite hormone replacement therapy, some patients continue to complain of overt signs and symptoms of hypothyroidism despite having normal labs that suggest these patients are given the correct dosage of levothyroxine (T4). In many cases, other factors such as comorbidities such as kidney failure, liver failure, adrenal abnormalities or psychiatric disorders, and medications, interfere with the optimal response, but in a few cases, there is no identifiable correlation with comorbidity and/or medication. We report the case of a 54-year-old Afro-Caribbean female who suffers from overt signs and symptoms of hypothyroidism, despite levothyroxine therapy and having normal labs that suggest she is receiving optimal doses of medication.

CASE REPORT

Chief complaint

Fifty four years old, Afro-Caribbean female complained of constant fatigue, dry skin, brittle hair and nails, cold intolerance, constipation, and unintentional weight gain despite no changes in appetite. The patient states that she has been suffering from these symptoms daily for the past 16 years, since the birth of her second child. The patient noted that for a few months she has had the sensation of a

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growth in her neck, where she feels like there is a fullness and sometimes “choking” feeling.

**Past medical history**
She was diagnosed with hypothyroidism in 1991 and underwent surgery in 1998 to remove part of each lobe after the patient was experiencing persistent shortness of breath for a few years due to glandular enlargement. The patient does not have any other significant medical history.

**Medications**
Currently, 175 mcg levothyroxine.
Initial dosage: 125 mcg levothyroxine since surgery, then increase to 150 mcg for 3 years.

**Past surgical history**

**Family history**
Father, 76 years of diabetes mellitus type II.

Mother, 74 years of hypertension, euthyroid goiter.

Sister, 57 years hypothyroidism, underwent total thyroidectomy for persistent gland enlargement.

Sister, 52 years hyperprolactinemia secondary to pituitary adenoma.

**Social history**
Denies smoking history and consumption of alcohol.

**Physical exam**

**General**
No acute distress.

HEENT: Normocephalic, PERRLA, EOMI, normal nasal mucosa, no tonsillar erythema or exudates.

Neck: slight thyroid prominence, no lymphadenopathy.

Chest: lungs clear to auscultation bilaterally.

Heart: RRR, normal S1 and S2, no rubs, murmurs or gallops.

Abdomen: normal bowel sounds, not tender to palpation, no rebound tenderness or guarding.

Extremities: Lower extremity varicosities noted bilaterally, mild hyperpigmentation of lateral malleoli bilaterally, DTRs present.

**DISCUSSION**
The thyroid secretes T4 and T3 in a ratio of about 11:1.[1] About 80% of the active thyroid hormone (T3) is produced through peripheral conversion within the cells of tissues by deiodinase enzymes. All tissues are exposed to the same concentration of free T4 and free T3 in the plasma, however, within the tissues; the concentration of free T3 varies since this is dependent on T4 transportation across cells and conversion through deiodinases.[1] Primary hypothyroidism is treated with levothyroxine or T4; this method of treatment is preferred because it can replace T4 in the circulation and cells can uptake and convert T4 to T3 based on needs. However, if there are problems with deiodination/conversion and transport on a cellular level, this treatment will not be effective.

Iodothyronine deiodinases are selenocysteine-dependent membrane proteins that are responsible for the conversion of T4 to T3 or rT3 in target cells. There are three isoforms of this enzyme, deiodinase type 1 (D1), deiodinase type 2 (D2), and deiodinase type 3 (D3). D2 catalyzes the formation of bioactive thyroid hormone by removing a single “outer-ring” iodine atom, and producing T3. D3 prevents T4 activation by removing a single “inner-ring” iodine atom producing rT3; to a greater extent it inactivates T3. D1 can activate or inactivate T4. D2 is more efficient at converting T4 to T3 compared to D1. 80–90% of T4 is converted to T3 in the pituitary gland; however, only about 30–50% is converted in the peripheral tissues;[3] this emphasizes the difference in efficiency of D1 and D2. The deiodinase enzymes, particularly D2 and D3, play integral roles in the homeostasis of thyroid hormones. D1 is found in many tissues, but predominantly in the liver and kidney, D2 in pituitary, brain, brown adipose tissue, and D3 in brain neurons. More than 50% of circulating T3 is produced extra-thyroidal by D1, with the major contribution produced by the liver.[4] The difference in activities of the deiodinase enzymes under varying conditions can explain the reason for tissue hypothyroidism, despite normal thyroid function tests. It is believed that D1 is suppressed and downregulated in response to physiologic and emotional stress, dieting, systemic illness, autoimmune disease, depression, obesity, inflammation, medications, and toxins; whereas the activity of D2 is not affected by these factors; therefore, there continues to be a normal production of T3 in the pituitary despite its reduction in peripheral tissues.[3] The activity of D2 in the pituitary gland is important in understanding the regulation of thyroid-stimulating hormone (TSH); the pituitary gland contains little D1 and no D3.[3] This means that a normal TSH level cannot reliably indicate the intracellular level of T3 in the peripheral tissues. There is also a limitation to the measurement of serum thyroid hormones because these levels do not correctly reflect intracellular levels of thyroid hormone.

Nutritional deficiencies can affect the conversion of T4 to T3 within cells by affecting the deiodinases, especially D1. There
are two nutritional deficiencies that are said to be contributory to imbalances in thyroid hormone, selenium (Se) deficiency, and iron deficiency. Compared to other organs in the body, the thyroid contains the highest amount of Se per gram of tissue.\[5\] Se is present in the form of selenocysteine in the active sites of all three deiodinases. Se deficiency appears to affect D1 more than D2, also it appears to affect some tissues, such as the liver, skin, and nonpregnant uterus more than other tissues;\[6\] the latter finding is said to be related to the ability of tissues to maintain their local concentrations of Se during deficient states. “...in liver, both Se levels, and deiodinase activity were greatly diminished; whereas in the cerebrum, thyroid, and pituitary, Se levels were decreased <50%, and deiodinase levels were well maintained.”\[6\] The effect that Se deficiency has on tissue conversion of T4 to T3 seems to be significant in severe deficiencies of this trace mineral; Bates et al. documented that a decrease of Se by more than 80% resulted in a marked decrease in deiodinase activity in the liver, skin, and uterus.\[6\] On the other hand, iron deficiency has a greater effect on reduction of thyroid hormone levels because of impaired production of thyroid hormones due to reduced activity of thyroid peroxidase and impaired conversion of T4 to T3 due to reduced activity of D1.\[7\]

Iron deficiency does not only cause impairment in thyroid peroxidase, which is a heme-containing enzyme in the thyroid that is necessary for the production of T4 and T3, resulting in a significantly lower concentration of T3, it also results in an increase in rT3 compared to normal.\[9\] An increase in rT3 demonstrates that D3 activity is increased in iron-deficient states and it results in competitive inhibition of thyroid receptors. Eftekhari et al. performed a study to determine if iron supplementation in iron-deficient Iranian adolescent girls would improve thyroid function and came to the following conclusion, “the iron-deficient participants in the placebo group showed 16, 9, and 11 lower levels of TT4, TT3, and T3RU and about 50% greater concentrations of rT3, after 12 weeks intervention in comparison to the iron-treated group.”\[9\] TSH concentration remains unaffected despite iron status; this attests to the finding that the intracellular levels of T3 in the pituitary are responsible for the feedback control of TSH. Iron deficiency anemia also results in decreased oxygen transport, which can impact the synthesis of thyroid hormones. Iodide is transported across the thyrocyte from the plasma through the sodium/iodide symporter or NIS. The iodide uptake is a sodium-dependent active transport process that couples the energy released by the inward movement of sodium down its electrochemical gradient to the simultaneous inward movement of iodide against its electrochemical gradient.\[10\] The sodium gradient is maintained by sodium-potassium ATPase, which requires oxygen to provide energy; therefore, iodide transport is energy-dependent, hence requiring oxygen.\[10\] Iodide is a necessary component in the synthesis of thyroid hormone, which occurs inside the thyroid gland.

D1 activity is reduced in states of chronic physiologic stress, whereas D2 and D3 activity increases; this results in a decrease in the conversion of T4 to T3 in most tissues, an increase in conversion in the pituitary, and an increase in production of rT3.\[11\] The effects of stress are related to cortisol; therefore, treatment with glucocorticoids will have the same effect, resulting in tissue hypothyroidism, causing potential weight gain, fatigue, and depression.\[3\] The generalized pattern of the effect of cortisol on thyroid hormone metabolism is, lowered TSH production, a blunted TSH response to thyroid-releasing hormone, a decrease in T3 and an increase in rT3.\[12\] With an increase in endogenous cortisol, there is decreased peripheral conversion of T4 to T3 and increased conversion of T4 to rT3.\[12\] Treatment with T4 will not help to alleviate these symptoms; however, it is proposed that supplementation with time-released T3 will.\[13\]

Inflammation is the body’s way of protecting itself from foreign bodies. Part of the response is the release of inflammatory cytokines interleukin 1 (IL-1), IL-6, C-reactive protein (CRP), and tumor necrosis factor-alpha. An increase in cytokine levels is seen in physical and emotional stress, chronic renal disease, diabetes, depression, menopause, heart disease, autoimmune diseases, injury, chronic infection, and cancer.\[6,13\] Inflammatory cytokines have an inhibitory effect on D1, which will reduce the conversion of T4 to T3 at the tissue. In their research, Xu et al. found a negative correlation of serum IL-6 concentration and rT3, whereas there is a positive correlation of serum IL-6 concentration and rT3,\[13\] which suggests a decrease in active thyroid function at the cells. Sharma et al. conducted a study to evaluate the correlation of CRP and thyroid hormones in neonates; they found a negative correlation between CRP concentrations and thyroid hormones, with no effect on TSH.\[14\] The importance of Se in the function of the deiodinases was explained earlier, however, Se also plays an important role in relieving oxidative stress in the body. Se is necessary for the activity of selenoproteins such as glutathione peroxidase (GSH-Px) and superoxide dismutase,\[15\] which function as antioxidant enzymes. A deficiency in Se has shown to result in a reduction in immune function. The importance of Se in improving the immune system has also a beneficial effect on the reduction of antibody load in autoimmune thyroiditis, a condition associated with euthyroidism or hypothyroidism that can be caused by a number of factors such as the presence of the cytotoxic T lymphocyte A4 promoter, iodide intake, immunotherapeutic agents, and viral infections.\[5\]

In patients with chronic renal failure, a combination of factors is believed to contribute to the effectiveness of selenoproteins, which include deiodinases and antioxidants (GSH-Px). These factors include the buildup of uremic toxins, increase in inflammatory cytokines, and oxidative stress, which all have an inhibitory effect on selenoproteins; resulting in a decrease in deiodinase and antioxidant activities. As established, the factors that have an inhibitory effect on D1 have the opposite
effect on D2, which is also observed for inflammatory cytokines. There is an observed increase in the activity of D2, which is known to normalize TSH concentrations despite a peripheral reduction in T3; this was also proven by Sharma et al., in their research, where elevated CRP levels resulted in a significant decrease in fT4 and fT3 with normal concentrations of TSH. Xu et al. showed that there was a positive correlation between rT3 and serum IL-6 concentration, which suggests that there is an increase in the activity of D3. Increase rT3 results in an increase in competitive inhibition of thyroid receptors, resulting in hypothyroid conditions.

The other important factor at the cellular level is the transport of thyroid hormones across the cell. It was believed that thyroid hormone entered cells by simple diffusion; this belief stemmed from the knowledge that iodothyronines are lipophilic compounds; therefore, they should easily cross the plasma membrane by simple diffusion. However, it is now known that the majority of thyroid hormone transport occurs through transmembrane transporters. There are several cellular transmembrane transporters identified that have a high affinity for thyroid hormone, however, with differences in tissue distribution and ligand affinities. Monocarboxylate transporter 8 (MCT8), MCT10 and organic anion transporting polypeptide (OATP) family have been explored more than the other transporters; therefore, they will be discussed below.

The exact mechanism by which MCT8 and MCT10 transport thyroid hormones are not fully understood. Polymorphisms are genetic variations that occur in the nucleotide sequence of the human genome of a small percentage of the population; it is possible that they may play a role in the differences of serum thyroid hormone levels between individuals. Polymorphisms of transmembrane transport of iodothyronines can result in tissue resistance of thyroid hormones. Polymorphisms differ from mutations in that polymorphisms are acceptable alternatives of a normal allele that is present in at least 1% of the population, whereas mutations are variations in the DNA sequence away from the normal that is present in <1% of the population. Table 1 provides a summary of the thyroid hormones transported by various cellular transmembrane transporters and the known polymorphisms of these transporters.

MCT8 is an active iodothyronine (T3 and T4) transporter encoded by the solute carrier family 16, member 2 gene, which is located on chromosome Xq13.2. This transporter is expressed in many tissues including, liver, kidney, heart, skeletal muscle, brain, and thyroid. The mutation of MCT8 results in Allan-Herndon-Dudley Syndrome; an X-linked syndrome that results in severe neurocognitive delay. This finding demonstrated the importance of MCT8 in the transport of thyroid hormone in the brain and the importance of thyroid hormone for brain development. The phenotypic effect of polymorphisms of the transporters also became of interest, given the drastic phenotypic effect of the mutation. Two polymorphisms of MCT8 have been identified; polymorphism rs6647476, which is a change of serine to Proline at position 107 (Ser107Pro) and rs5937843, which represents a change from base guanine to thymine (G >T). These studies demonstrated no effect or an inconsistent effect of these polymorphisms on serum thyroid hormone levels.

MCT10 is an active iodothyronine transporter that is homologous to MCT8. It is located on chromosome 6121-q22 and is expressed in the kidney, skeletal muscle, placenta, heart, and small intestines. Unlike MCT8, in addition to the transport of iodothyronines, MCT10 also transports

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Hormones transported</th>
<th>Polymorphism</th>
<th>Change</th>
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<tbody>
<tr>
<td>MCT8</td>
<td>T4, T3</td>
<td>rs6647476</td>
<td>Ser107Pro</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rs5937843</td>
<td>G &gt;T</td>
</tr>
<tr>
<td>MCT10</td>
<td>T4, T3</td>
<td>rs14399</td>
<td>C &gt;A</td>
</tr>
<tr>
<td>OATP1A2</td>
<td>T4, T3, rT3</td>
<td>rs57921276</td>
<td>Ile13Thr</td>
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<td></td>
<td></td>
<td>rs57550534</td>
<td>Glu172Asp</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>T4S, T3S, rT3S</td>
<td>rs4149056</td>
<td>Val174Ala</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>rT3, T4S, T3S, rT3S</td>
<td>rs4149117</td>
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</tr>
<tr>
<td>OATP1C1</td>
<td>T4, rT3, T4S</td>
<td>rs7311358</td>
<td>Met233Ile</td>
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<td>rs10770704</td>
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<td>C3035T</td>
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Source: http://jme.endocrinology-journals.org/content/44/1/1/T4.expansion.html
Aromatic amino acids, and it appears that it plays more of a critical role in the export than the import of aromatic amino acids.\textsuperscript{[15,17]} Along with cellular uptake, MCT8 and MCT10 also facilitate the efflux of iodothyronines, and it is believed that the cellular uptake of thyroid hormone by MCT10 may be driven by the efflux of aromatic amino acids. Mutations of MCT10 have not been yet identified; however, there is one polymorphism noted, rs14399, which represents a change of cytosine to alanine (C >A).\textsuperscript{[20]} In comparison to the polymorphisms of MCT8, an effect of this change on the levels of serum thyroid hormone has not been observed, and phenotypic effects related to this change have not been noted.\textsuperscript{[15]} Despite there being no identified mutations of MCT10, it is theorized that mutations can significantly impair tissue uptake of T3.\textsuperscript{[21]}

The OATPs are a group of transporters responsible for sodium-independent transmembrane transport of amphipathic organic compounds, however, of the family, members of the OATP1, OATP4, and OATP6 subfamilies have been identified as facilitators of thyroid hormone uptake.\textsuperscript{[15]} The best-understood subfamily is OATP1, which includes OATP1A2, OATP1B1, OATP1B3, and OATP1C1.\textsuperscript{[15]}

OATP1A2 is expressed in liver, brain, and kidney and is responsible for the transport of T4, T3, and rT3.\textsuperscript{[15,22]} Given the low specificity of this transporter, it is thought to serve as a substitute transport system in case of malfunction or saturation of other transporters.\textsuperscript{[15]} There are two identified polymorphisms of OATP1A2, rs57921276 which is a change of isoleucine to threonine at position 13 (Ile13Thr) and rs57550534 representing a change of glutamine to aspartate at position 172 (Glu172Asp).\textsuperscript{[23]} For both polymorphisms, there has not been any effect observed on the levels of serum thyroid hormone. No significant effect of these polymorphisms on the phenotype has been identified.

OATP1B1 and OATP1B3 are homologous and expressed only in the liver.\textsuperscript{[4,6]} OATP1B1 stimulates the uptake of the only iodothyronine sulfates T4S, T3S, and rT3S, which are the waste products of iodothyronines T4, T3, and rT3.\textsuperscript{[23]} On the other hand, in addition to the transport of iodothyronine sulfates, OATP1B3 also transports rT3.\textsuperscript{[15]} Polymorphism rs4149056 has been the only polymorphism identified for OATP1B1, and it represents a change of valine to alanine at position 174 (Val174Ala). This polymorphism resulted in higher levels of T4S and a lower T3/rT3 ratio.\textsuperscript{[23]} There have been two identified polymorphisms for OATP1B3, rs4149117 that represents a change of serine to alanine at position 112 (Ser112Ala) and rs7311358 that represents a change of methionine to isoleucine at position 233 (Met233Ile).\textsuperscript{[15]} Both polymorphisms have not shown to have an effect on serum thyroid hormone levels, and there have not been any documented phenotypic effects of these polymorphisms.

OATP1C1 is the only member of the OATP transporters that have shown a high preference for T4 and rT3 and it is almost exclusively expressed in the brain.\textsuperscript{[15]} To a lesser degree, it is also responsible for the uptake of T4S.\textsuperscript{[15]} A study conducted by Sugiyama et al. demonstrated that in hypothyroid rats, OATP1C1 is upregulated, whereas it is downregulated in hyperthyroid rats.\textsuperscript{[24]} Due to the critical role of thyroid hormone in brain homeostasis, D2 and OATP1C1 expression vary to counteract the alterations in serum T4, ensuring stable concentrations of hormone in the brain. The following polymorphisms of OATP1C1 transporter have been identified: rs10770704, representing a change of base cytosine to thymine (C >T), rs36010656, a change of Proline to threonine at position 143 (Pro143Thr) and rs10444412, and a change of cysteine to threonine at position 3035 (C3035T).\textsuperscript{[23]} Van der Deur et al. studied 141 patients with primary autoimmune hypothyroidism, adequately treated with levothyroxine monotherapy, and discovered that despite therapy these patients continued to have persistent fatigue and depression. The results of the study showed that polymorphisms C >T and C3035T were associated with symptoms of fatigue and depression.\textsuperscript{[23]} It was also observed that the three identified polymorphisms of OATP1C1 did not have any effect on serum thyroid hormone levels.\textsuperscript{[15]} In a recent review, Panicker has shown that most of the associations between polymorphisms in thyroid hormone pathway genes and thyroid hormone-related endpoints were independent of serum thyroid hormone levels, which highlight the importance of local regulation of thyroid hormone in tissues.\textsuperscript{[15]} This finding further highlights the concern of tissue resistance despite adequate hormone replacement therapy, as confirmed by normal serum thyroid hormone levels.

The patient in the case presentation is euthyroid, based on lab tests done in 2006 and 2014, as shown in Table 2. Lab tests were done in 2016 after there was an increase in levothyroxine to 175 mcg for controlling the enlarging gland, based on physical examination and patient’s complaints of choking sensation. These lab tests suggested that the patient was receiving too much levothyroxine; despite these changes, she continued suffering from signs and symptoms of hypothyroidism. Tissue resistance, due to polymorphisms of transporters, is a plausible explanation for the persistent symptoms in this patient. The theory of the control of TSH by the local concentration of pituitary thyroid hormones can explain the normal TSH, and the changes in TSH values as the strength of T4 increased. Serum FT3 was within the normal range in all labs; as it was stated by Beard et al., the major contributor to circulating T3 is the liver.\textsuperscript{[4]} Of all the tissues, the liver contains the most thyroid hormone transporters, MCT8, OATP1A2, OATP1B1, and OATP1B3, therefore, if there is a polymorphism of one or even two transporters, the transport of thyroid hormone in the liver can be compensated by the other functional transporters, whereas the effect will be
evident for other cells in the body. In 2016, FT4 was elevated above the normal range; it would be expected that FT3 would also be increased above the normal range; however, FT3 remained within normal ranges, which is suggestive of limited T4 transportation across the membrane and limited conversion into T3. Another factor that should be taken into account is the difference in the number of transporters among varying cells; which can possibly explain why some tissues receive more active thyroid hormone and other tissues do not, therefore some symptoms may persist while others may abate. In addition to possible polymorphisms of transporters, as the patient’s symptoms continued, her weight significantly increased, BMI 39.3. As stated earlier, obesity is a factor that is believed to suppress and downregulate the activity of D1, resulting in a reduction in the production of T3 in peripheral tissues. The effects of suffering from hypothyroidism despite levothyroxine replacement become a vicious cycle; however, treating the underlying cause, which is believed to be transporter polymorphisms in this patient, should resolve the patient’s unintentional weight gain and thus abate the cycle.

There are several limitations to proving tissue resistance due to transporter polymorphisms, for the persistent hypothyroid symptoms: All thyroid hormone transporters along with tissue distribution and all transporter polymorphisms have not been identified, the phenotypic effect of known transporter polymorphisms is not clearly understood, and there are no tests available to determine the local cellular concentration of thyroid hormones. Unfortunately, until there are concrete answers to these unknown factors, there is a reliance on trial and error of using different medications such as cytomel, which contains T4 and T3 and assessing the patient’s symptoms. Furthermore, a significant limitation to this study was the scarcity of research that explains the association of polymorphisms in the deiodinase transmembrane transporters and receptors with clinical endpoints and how these polymorphisms affect treatment with standard levothyroxine therapy.

CONCLUSION

There are many factors that can affect the treatment of hypothyroidism with the standard levothyroxine replacement therapy; of these factors, the phenotypic effect of transporter polymorphisms needs to be further investigated and understood, as this would be the most difficult factor to overcome. When treating patients with hypothyroidism, physicians should not only be concerned about the lab values but also the complaints of the patient, as tissue hypothyroidism may be a reason for persistent signs and symptoms of hypothyroidism.

DECLARATION OF INTEREST

There are no conflicts of interest to declare.

PATIENT CONSENT

Written informed consent was obtained from the patient for publication of the submitted article and accompanying labs.

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