Low cholesterol levels are good markers for central hypothyroidism in case with dialysis using roxadustat

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Data availability statement

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Conflict of interest disclosure

The authors state that the study was conducted without any commercial or financial relationships that could be interpreted as a conflict of interest.

Ethics approval statement

All procedures performed in studies involving human participants were by the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable thical standards.

Permission to reproduce material from other sources Not applicable.

Clinical trial registration Not applicable.

Key Clinical Message

Recently, hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors have been used for renal anemia, but side effects have also been reported. We report on the association of central hypothyroidism and cholesterol with roxadustat.

INTRODUCTION

Renal anemia is an avoidable and critical complication in cases of chronic renal failure. A recombinant human EPO (rHuEPO) has given a privilege to chronic kidney disease (CKD) patients from blood transfusions, but there are also some difficulties such as pain when administering the drug injection and the complexity of handling the drug for injection. In recent years, hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors, which are orally administrable drugs for treating renal anemia, have been used [1]. The drug induces erythropoietin production via HIF, reducing the difficulties in renal amenia patients with rHuEPO injection. However, along with the many benefits, cautions have also been pointed out when using HIF-PH inhibitors. There are some concerns about its effects on cancer cells and retinal hemorrhage [2-4]. Roxadustat is an oral HIF-PH inhibitor that stimulates erythropoiesis. Here, we showed a case of central hypothyroidism caused by roxadustat with a summary of our similar cases. To find out central hypothyroidism, low cholesterol levels were good markers.

CASE REPORT

A sixty-nine-year-old male started hemodialysis in 2017 due to diabetic kidney disease. Roxadustat (a HIF-PH inhibitor) was started at a dose of 100mg for recombinant human EPO-resistant anemia in August 2020. The dose of roxadustat was increased to 200 mg to improve his anemia. TSH and fT4 were within the normal range during recombinant human EPO administration. General malaise gradually developed after starting roxadustat. His TSH and fT4 gradually decreased to 0.47μIU/mL and 0.15 ng/dL, respectively. Furthermore, cholesterol levels were markedly low (Total-C 84 mg/dL, HDL-C 48 mg/dL, LDL-C 31 mg/dL). Levothyroxine (a synthetic thyroxine) was started at a dose of 12.5 μg for hypothyroidism in February 2021 and was admitted to the hospital for further examination. Oral medications at an administration were levothyroxine, antihypertensive drugs, and antiplatelet drugs. There was no fever or hypothermia, blood pressure was 160/84 mmHg, and pulse rate was 78 beats/minus. There were no abnormal physical findings, including thyroid.

Laboratory data is shown in Table 1. Thyroid-related auto-antibodies were negative. No abnormalities were observed in other pituitary hormones. Brain MRI revealed no abnormality in the pituitary gland. A TRH stress test was performed and the patient was diagnosed with central hypothyroidism (Table 2).

The dose of levothyroxine was increased for central hypothyroidism. After administration of 200 μg of levothyroxine, fT4 recovered quickly into the normal range, but TSH did not recover. Central hypothyroidism might be speculated as an adverse effect of roxadustat. In January 2021, roxadustat was switched to daprodustat (Fig.1). After discontinuing roxadustat, TSH recovered rapidly into the normal range. Moreover, cholesterol levels increased. TRH test was performed again, and the results were normal. Therefore, central hypothyroidism was reversible. Levothyroxine was tapered and discontinued, but thyroid function remained within the normal range.

DISCUSSION

We present a case of a dialysis patient who developed central hypothyroidism after using roxadustat. Table

3 is a summary of central hypothyroidism dialysis patients taking roxadustat at our hospital. All cases decreased TSH and fT4 after taking roxadustat. Roxadustat was discontinued in 7 patients, and the dose was reduced in 1 patient, TSH and fT4 recovered. Although central hypothyroidism by roxadustat might be reversible, it takes a longer time to recover thyroid function, if thyroid hormones are severely suppressed for a long period. Therefore, early detection of central hypothyroidism is required. Markedly reduced cholesterol levels would be good markers to speculate hypothyroidism. The decreased cholesterol levels were recovered in all cases after discontinuing or reducing roxadustat in a similar way to recover thyroid function.

The central hypothyroidism in our case was reversible. And the central hypothyroidism would depend on taking roxadustat. Similar cases were reported previously [2,4]. Some drugs, such as retinoid X receptor selective ligands, have been reported to suppress TSH gene promoter activity, thereby causing central hypothyroidism [5]. Therefore, it is speculated that roxadustat caused central hypothyroidism by a similar mechanism. Another possibility is the direct effect on the thyroid hormone receptor. Roxadustat has a similar chemical structure to T3. It would have a stronger affinity for the thyroid hormone receptor TRβ than T3 [6]. Thereby, it acts as an agonist on the thyroid hormone receptor TRβ present in the hypothalamus and pituitary gland, suppressing TSH secretion. Additionally, it has been reported that roxadustat may partially cross the blood-brain barrier in mice [7]. Therefore, it is possible that orally administered roxadustat crosses the blood-brain barrier, and binds to thyroid hormone receptor TRβ. These are possible mechanisms of central hypothyroidism after using roxadustat.

In our case, cholesterol levels were markedly reduced in the condition of central hypothyroidism. Thyroid hormones have important effects on cell development, growth, and metabolism, and are expressed and act in almost all tissues [8,9]. Thyroid hormone binds to thyroid hormone receptors in the nucleus and lowers cholesterol levels through TRβ. TRβ stimulation increases LDL receptor expression in the liver, resulting in plasma clearance of LDL cholesterol [10]. As described previously, it is speculated that roxadustat binds to TRβ [6], increases the expression of LDL receptors, and lowers cholesterol. Therefore, it is speculated that reduced cholesterol levels are an agonistic effect of roxadustat on the TRβ1 receptor in the liver. All of the seven cases, including the present case, showed significant cholesterol reduction during treatment with roxadustat, which improved after discontinuation or reduction of the drug. Hypocholesterolemia is presumed to be a TRβ-mediated effect similar to the TSH secretion effect of roxadustat in the brain, so the detection of hypocholesterolemia is an important marker for finding central hypothyroidism.

We experienced a dialysis case with hormonal dynamics similar to central hypothyroidism caused by roxadustat. A decrease in cholesterol was observed during the administration of roxadustat, and the patient developed symptoms after discontinuing roxadustat. The TRH stress test after discontinuing the drug showed a normal response, and this condition was judged to be a reversible change. It was speculated that roxadustat acts suppressively as an agonist in the hypothalamus and pituitary gland, and as an agonist in target organs.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

All the authors have declared no competing interests.

Ethical approval

All procedures performed in studies involving human participants were by the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Consent for publication

Informed consent was obtained from the individual for the publication of any potentially identifiable images included in this article.

Conflict of Interest

The authors state that the study was conducted without any commercial or financial relationships that could be interpreted as a conflict of interest.

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FIGURE LEGEND

Fig 1. Clinical course of the case

TSH and fT4 were within the normal range during recombinant human EPO administration. After starting roxadustat, his TSH and fT4 gradually decreased to 0.47μIU/mL and 0.15 ng/dL, respectively. After administration of 200 μg of levothyroxine, fT4 recovered quickly into the normal range, but TSH did not recover. In January 2023, roxadustat was switched to daprodustat. After discontinuing roxadustat, TSH recovered rapidly into the normal range and and cholesterol levels increased to their original levels.

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