Improvement in polycythaemia vera after parathyroidectomy for primary hyperparathyroidism

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Dear Sir,

We report a case of a woman who was diagnosed with primary hyperparathyroidism two years after being diagnosed with polycythaemia vera (PV). She was found to have a parathyroid adenoma that was successfully removed surgically, confirmed by a drop in her parathyroid hormone levels. After parathyroidectomy, she showed a significant improvement in her PV.

A 59-year-old woman with hypertension showed a persistently elevated haemoglobin and haematocrit level during routine follow-up. She did not have any symptoms of hyperviscosity, any history suggestive of a secondary cause of polycythaemia, or any other malignancy. Examination revealed a plethoric female with no hepatosplenomegaly. Laboratory investigations revealed a haemoglobin level of 22.7 g/dL and haematocrit level of 0.71%. A positive JAK2 V617F mutation and a low erythropoietin level confirmed the diagnosis of PV as per the World Health Organization’s diagnostic criteria.\(^1\) Subsequently, the patient was started on tablet hydroxyurea 500 mg daily with regular phlebotomy. Her haemoglobin levels were maintained at 13.5–15.8 g/dL, with no complications. She required removal of 300–400 mL of blood every 60–90 days.

Two years later, the patient started to complain of frequent headaches, polyuria and constipation. Her haemoglobin level at that point was 15.8 g/dL. Upon evaluation, she was found to have parathyroid-dependant hypercalcaemia, with an adjusted calcium level of 2.9 mmol/L and an intact parathyroid hormone (PTH) level of 11.6 pmol/L (Table I). Serum phosphate and other electrolytes were within the normal range. Her renal function and alkaline phosphatase level were also within the normal range, along with a normal calcium/creatinine clearance ratio. Her vitamin D level was 42 nmol/L, for which she was started on vitamin D3 2000 U daily. She underwent neck ultrasonography and a Technetium (99mTc) sestamibi parathyroid imaging, and both imaging techniques detected a left upper pole parathyroid
adenoma. The patient was diagnosed with symptomatic primary hyperparathyroidism secondary to a parathyroid adenoma and was advised to undergo parathyroidectomy.

Table I. Serial measurement of calcium with haematocrit.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Reference interval</th>
<th>Month/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>12.0–15.0</td>
<td>22.7</td>
</tr>
<tr>
<td>Haematocrit (L/L)</td>
<td>0.4–0.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.2–2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>iPTH (pmol/L)</td>
<td>1.3–6.8</td>
<td>11.6</td>
</tr>
</tbody>
</table>

*Surgery completed. iPTH: intact parathyroid hormone

Intraoperatively, a left superior parathyroid adenoma was identified and the gland was excised, while the three remaining normal glands were preserved. Intraoperative PTH levels were used as the baseline, and successful removal of the pathological gland was confirmed, with a more than 50% decline in PTH level after excision compared to the pre-excision value (pre-incision: 18.0 pmol/L, pre-excision 12.1 pmol/L, post-excision 5.3 pmol/L; reference interval 1.3–6.8 pmol/L). The patient did not have any significant postoperative hungry bone syndrome, as she had undergone pre-emptive replacement with activated vitamin D before surgery. Histopathologic examination of this nodule confirmed the diagnosis of parathyroid adenoma. Postoperatively, the patient had an adjusted calcium level of 2.4 mmol/L, and her PTH level was 5.3 pmol/L on Postoperative Day 2. Of note, her haemoglobin levels remained at 14.2–14.8 g/dL with continuation of low-dose hydroxyurea only, with no further venesection required. Fig. 1 shows her calcium and haematocrit levels before and after parathyroidectomy.
Fig. 1 Chart shows calcium and haematocrit levels of the patient before and after parathyroidectomy.

Our case represents an association between PV and primary hyperparathyroidism. Although there have been case reports of a similar association, it is not known to be common. The first case of hyperparathyroidism associated with polycythaemia was reported by Berlin in 1949.\(^2\) Thereafter, Fallah et al, in their analysis, found a two-fold increased risk of PV after parathyroid adenoma (five-fold in men) and a higher risk of parathyroid adenoma after PV (about eight-fold in men and three-fold in women).\(^3\)

The relationship between PV and primary hyperparathyroidism continues to be of interest, as few reports have described the remission of PV following parathyroidectomy, as in our case.\(^4\) Similar associations have been reported, suggesting a causal link between PTH and PV, which is clinically significant.\(^5,6\)

The parathyroid tumour may have produced or induced the production of a growth factor that can stimulate pancytosis.\(^7\) Tiryakioglu et al suggested that the calcium-PTH axis is important for the activation of erythropoiesis.\(^8\) Yao et al showed that bone marrow mesenchymal stromal cells are involved in the haematopoiesis-stimulating effects of PTH via
upregulation of cadherin-11.\(^9\) However, the relationship between PTH and myeloproliferative disorders is not yet completely understood.

Meytes et al found that calcium infusion or PTH administration significantly increased the mitotic activity of bone marrow within a few hours, followed by an increase in reticulocyte production, suggesting stimulation of erythropoiesis; however, clinical observations support a role of excess PTH in the pathogenesis of the anaemia of renal disease, supporting the evidence that PTH has an inhibitory effect on erythropoiesis.\(^{10}\)

The available data suggests that stimulation or inhibition of erythropoiesis may be related to the amount of calcium available to the cells, and the duration of excess PTH may play a role. In our patient, polycythaemia preceded the presentation of primary hyperparathyroidism by two years. This indicates that she might have had asymptomatic primary hyperparathyroidism prior to the diagnosis of PV.

Our patient had significant polycythaemia, requiring phlebotomy of 300–400 mL every 2–3 months, in addition to hydroxyurea prior to parathyroidectomy. After parathyroidectomy, the haematocrit values were maintained within the normal range without any further phlebotomy, and the dose of hydroxyurea was gradually reduced without any adverse effect on the haematocrit. This strongly suggests the presence of a causal relationship between the primary hyperparathyroidism and the polycythaemia.

Although there have been reports of complete resolution of PV after parathyroidectomy, Kulaylat et al have described a case with PV and primary hyperparathyroidism, wherein improvement in the patient’s haemoglobin level proved to be transient after parathyroidectomy. Their patient was Janus kinase (JAK) 2 negative, unlike our patient, who was JAK2 positive.\(^{11}\) The JAK/signal transducers and activators of transcription pathway play a central role in initiating signal transduction from hematopoietic growth factor receptors. JAK2 is directly involved in intracellular signalling in PV progenitor cells, a process
that occurs after exposure to cytokines to which these cells are hypersensitive. This raises the question of whether the presence of JAK2 mutation differentiates between patients with polycythaemia who might respond to parathyroidectomy and those who might not.

Associations between PV and hyperparathyroidism have been described in the literature. Our case provides further evidence that this association is of clinical significance in view of improvement of our patient’s PV after removal of the parathyroid adenoma. Thus, it remains imperative that patients with PV be screened for primary hyperparathyroidism. Further studies are warranted on the possible role of JAK2 mutation in the calcium-PTH axis and the effect of PTH on haematopoiesis.

Yours sincerely,

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