CASE REPORT

Hypersomatotropism induced secondary polycythaemia leading to spontaneous pituitary apoplexy resulting in cure of acromegaly and remission of polycythaemia: 'The virtuous circle'

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SUMMARY

A young man with subtle clinical features suggestive of hypersomatotropism presented with acute-onset severe headache. Relevant investigations confirmed polycythaemia and growth hormone (GH)-secreting pituitary macroadenoma with apoplexy. Secondary polycythaemia and myeloproliferative disorders were ruled out. At follow-up after 3 months, resolution of polycythaemia and acromegaly was observed, evident on normal haemoglobin levels, a normocellular marrow, and normal insulin-like growth factor-1 (IGF-1) with glucose-suppressed GH levels. Direct mitogenic properties of GH-IGF-1 axis on bone marrow progenitor cells may very rarely lead to erythroid hyperplasia and subsequent polycythaemia, reversible with successful therapy of acromegaly. In this case, polycythaemia secondary to hypersomatotropism likely resulted in pituitary apoplexy with subsequent remission of both acromegaly and resultant polycythaemia.

BACKGROUND

Polycythaemia can be primary, secondary to underlying hypoxaemia due to certain clinical conditions or relative, which is associated with a contraction of plasma volume without an absolute increase in red cell mass, an entity known as spurious polycythaemia (Gaisbock's syndrome). Primary polycythaemia or polycythaemia rubra vera (PRV) is diagnosed by the WHO criteria revised in 2016.¹ Chronic smoking, congenital cyanotic heart diseases, haemoglobinopathies, chronic lung diseases and obstructive sleep apnoea are some of the commonly encountered secondary causes of polycythaemia, in which circulatory erythropoietin (EPO) level is elevated. Haematological abnormalities mainly related to white blood cell alterations have seldom been encountered in acromegaly²; even rarer is involvement of red cell lineage. In a retrospective analysis of 141 acromegalics, only one patient had polycythaemia while anaemia, on the contrary, was far more common.³ In acromegaly, polycythaemia is mostly observed due to chronic hypoxia secondary to obstructive sleep apnoea but to a lesser extent due to an underlying EPO-secreting renal neoplasm.³ The occurrence of PRV in acromegaly is exceedingly rare and such association has been documented in exceptional cases.⁴

CASE PRESENTATION

A 36-year-old normotensive, normoglycaemic, non-smoker man presented to the casualty with sudden-onset, severe, non-remitting, holocephalic headache which had commenced 5 days prior to the current presentation. Clinical examination revealed a Glasgow Coma Scale of 15 with mild prognathism, prominent supraorbital ridges, broad nose, thick lips, plethora of bilateral lower palpebral conjunctiva, hyperhidrosis, oily skin, spade-shaped large hands and large feet (figures 1–3). There was no history suggestive of aquagenic pruritus or obstructive sleep apnoea. The rest of systemic examination including confrontation perimetry was unremarkable. Complete blood count revealed polycythaemia with normal white cell count ($5.1 \times 10^9/L$) and platelet count ($185 \times 10^9/L$). In view of disabling headache, a non-contrast CT of brain was done which was unremarkable, except for a probable sellar mass. MRI of hypothalamo-pituitary region revealed a sellar mass ($26 \text{ mm} \times 21 \text{ mm} \times 15 \text{ mm}$) abutting the optic chiasma, but without any enhancement on gadolinium contrast. The mass was hyperintense in T1-weighted and hypointense in T2-weighted sequences suggestive of pituitary macroadenoma with apoplexy (early subacute stage; 3–7 days) (figure 4). Subsequent endocrinological evaluation established hypersomatotropism with multiple pituitary hormone deficiencies. A true erythrocytosis was confirmed by an increased red cell mass. Relevant investigations have been summarised in table 1.

TREATMENT

The patient underwent a single session of peripheral phlebotomy with removal of 300 mL of venous blood to avoid potential fatal consequences arising due to polycythaemia. To reduce the risk of thrombosis, compression stockings and intermittent pneumatic compression device were used. The patient was further managed with intravenous hydrocortisone (200 mg/day in four divided dosages) initially, followed by oral hydrocortisone (15 mg/day) and levothyroxine (50 mcg/day).

OUTCOME AND FOLLOW-UP

The patient did pretty well with conservative management. Three months after his initial

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Figure 1 Thick lips, broad nose and prognathism suggestive of hypersomatotropism.

presentation, conjunctival plethora and hyperhidrosis subsided (figure 5) while a repeat bone marrow biopsy documented a normocellular marrow. In view of pituitary apoplexy and subsequent normal insulin-like growth factor-1 (IGF-1) levels with glucose-suppressed growth hormone (GH) at 3 months (table 1), therapy for acromegaly (either surgical or medical) was not considered.

DISCUSSION

According to the WHO, diagnosis of PRV requires meeting either all three major criteria (elevated haemoglobin/haematocrit, pancytopenia in bone marrow biopsy and presence of JAK2V617F or JAK2 exon 12 mutation) or the first two major

Figure 2 Plethora of lower palpebral conjunctiva at presentation.

Figure 3 Broad spade-shaped hand suggestive of acromegaly.

criteria and the minor criterion (subnormal serum EPO level). In this patient, systemic evaluation was done according to the guidelines; however, no evidence of clonal myeloproliferative disorder like PRV was apparent. Moreover, the prompt resolution of polycythaemia following pituitary apoplexy with normalisation of IGF-1 and glucose-suppressed GH levels at 3 months' follow-up confidently ruled out the possibility of such a neoplastic disorder.

Low normal EPO effectively eliminated secondary causes of polycythaemia as well. Subtle clinical features of hypersomatotropism and pituitary 'incidentaloma' prompted appropriate endocrinological evaluation which ultimately confirmed GH-secreting macroadenoma.⁵ Polycythaemia has also been reported in association with functional luteinising hormone-secreting pituitary adenoma with elevated testosterone and Cushing's disease.⁶ However, hormonal evaluation effectively ruled out such possibilities in our case.

GH and IGF-1 have mitogenic property which perhaps explains the increased incidence of cancers in acromegaly and in occasional patients receiving long-term supraphysiological GH replacement therapy. GH-IGF-1 axis probably also regulates bone marrow cell growth and differentiation.^{7,8} Normocytic normochromic anaemia and impaired erythroid proliferation in GH deficiency, subsequent restoration of normal haemoglobin levels with GH therapy and reversible elevation of plasma volume and red blood cell volume observed in some patients with acromegaly support this hypothesis.

Elevated GH and/or IGF-1 possibly acting in synergy with yet unknown host factors or hypersensitivity of bone marrow

Figure 4 MRI (sagittal sections) of hypothalamo-pituitary area showing pituitary macroadenoma abutting optic chiasma which is predominantly hyperintense in T1-weighted (A) and hypointense in T2-weighted (B) sequences suggestive of apoplexy in early subacute phase. The white arrow in panel (A) denotes pituitary tissue.

Table 1 Summary of investigations done at baseline and follow-up visits

Parameter	Age and sex-specific reference range	At diagnosis	At 2 weeks	At 3 months
Haemoglobin (g/dL)	13.3–16.2	20.1	14.0	11.2
Haematocrit (%)	38.8–46.4	61.3	42.4	37.8
Erythropoietin (EPO) (mIU/mL)	4–27	4.23		
Insulin-like growth factor-1 (IGF-1) (ng/mL)	115–307	516		160
Growth hormone (GH) (post-75 g glucose at 1 hour) (ng/mL)				0.3
GH (post-75 g glucose at 2 hours) (ng/mL)				0.36
Cortisol (08:00) (µg/dL)	5–25	0.4		
Thyroid-stimulating hormone (TSH) (µIU/mL)	0.34–4.25	0.07		
Free T4 (ng/dL)	0.89–1.76	1.26		
T3 (ng/dL)	60–180	118		
Prolactin (ng/mL)	2.5–17	3.03		
Testosterone (ng/dL)	270–1070	14		
Luteinising hormone (LH) (mIU/mL)	2–12	1.02		
Follicle-stimulating hormone (FSH) (mIU/mL) (pooled sample)	1–12	1.39		

Arterial blood gas analysis at presentation (PaO₂: 94 mm Hg, pH: 7.41, pCO₂: 44 mm Hg, bicarbonate: 24 meq/L).

Bleeding time (BT), clotting time (CT), prothrombin time (PT) and activated partial thromboplastin time (aPTT): normal.

Abdominal ultrasonography, spirometric pulmonary function test, haemoglobin electrophoresis, ECG, echocardiogram (M and 2D mode) and polysomnography: normal. JAK2 V617F and JAK2 exon 12 mutation: negative.

Bone marrow biopsy examination revealed hypercellular marrow with erythroid hyperplasia without granulocytic or megakaryocytic proliferation.

progenitor cells to GH and/or IGF-1 due to an idiosyncratic host condition leading to a direct reversible proliferative effect on erythropoiesis has been speculated to explain the occurrence of reversible polycythaemia in acromegaly. To the best of our knowledge, only one case report has so far advocated the direct proliferative effects of GH-IGF-1 axis on bone marrow progenitor cells leading to erythropoiesis, which was reversible with octreotide therapy.³

Myeloproliferative disorders like PRV and essential thrombocytosis may at times lead to haemorrhagic diathesis.⁹ The

Figure 5 Disappearance of conjunctival plethora at 3 months.

pathophysiology and underlying risk factors, if any, of spontaneous bleeding in these conditions have not been elucidated but elevated platelet count with an acquired von Willebrand syndrome has been hypothesised to be the likely explanation.¹⁰ Often, a pituitary macroadenoma may undergo spontaneous apoplexy, which might be another possible explanation in our case.

The Endocrine Society recommends trans-sphenoidal surgery as the primary therapy in most patients with acromegaly and acknowledges that the experience of the surgeon is the major determinant in achieving successful outcomes after pituitary surgery. However, even with experienced pituitary surgeons operating in well-equipped centres, trans-sphenoidal micro-surgery results in an initial remission rate of 40%–50% for macroadenomas.¹¹ Needless to state, this figure is much lower in inexperienced hands as we observe in our practice and many of our patients have to undergo pituitary radiation therapy after an unsuccessful surgery. Pituitary apoplexy can result in complete cure in some fortunate patients with GH-secreting pituitary macroadenoma where nature itself performs the role of a successful surgeon obviating the need for postoperative medical therapy and/or radiotherapy.¹² Hormonal evaluation done at 3 months' follow-up visit was suggestive of cure of acromegaly in our patient.¹³

In light of the above considerations, we believe polycythaemia in our patient was a result of the direct but reversible mitogenic effect of elevated circulatory GH/IGF-1 on bone marrow erythroid precursor cells. Pituitary apoplexy in this patient was likely a manifestation of polycythaemia that led to cure of acromegaly, which in turn resulted in remission of polycythaemia.

Learning points

- Polycythaemia can be primary, secondary to underlying hypoxaemia or relative, associated with contraction of plasma volume without an absolute increase in red cell mass, an entity known as spurious polycythaemia (Gaisbock's syndrome).
- Polycythaemia rarely encountered in acromegaly is usually secondary to obstructive sleep apnoea or an underlying erythropoietin-secreting renal neoplasm or a myeloproliferative disorder.
- Very rarely, the direct proliferative effects of growth hormone-insulin-like growth factor-1 axis on bone marrow progenitor cells may lead to erythropoiesis, reversible with medical or surgical therapy.
- Polycythaemia can occasionally lead to bleeding diathesis. The occurrence of pituitary apoplexy due to polycythaemia secondary to hypersomatotropism may lead to spontaneous remission of acromegaly and the resultant polycythaemia, obviating the need for any further therapeutic intervention.

Contributors SP, SNB, JD and PPC were involved in diagnosis and management of the patient. SP, SNB and PPC were involved in literature search and writing of the manuscript.

Competing interests None declared.

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