

## A Case of Paraganglioma Presenting as Polycythemia in a Young Patient: A Case Report

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Hypertension; Paraganglioma; Polycythemia

**1. Abstract**

**1.1. Background:** Erythrocytosis may result from primary or secondary causes. Primary erythrocytosis results from abnormalities that lead to constant overproduction of red cells and low erythropoietin (EPO) levels. EPO-producing tumors such as hepatocellular carcinoma and renal cell carcinoma are well known secondary causes. Paragangliomas are rare tumors characterized by increased release of catecholamines with symptoms more commonly hematuria, hypertension, headache and post-micturition syncope. Moreover, paragangliomas are largely associated with genetic mutations, with new mutations constantly being discovered.

**1.2. Case Report:** A 14-year-old female presented to our clinic with sweating, palpitations, and palmar erythema. The patient's history was significant for uninvestigated hypertension diagnosed at the age of 9. Blood investigations revealed elevated hemoglobin levels of 18.5 g/dL and hematocrit of 57.5%. Whole genome sequencing found no mutations, excluding polycythemia vera from the differential diagnosis. Computed tomography (CT) revealed two lesions compatible with urinary bladder paragangliomas and retroperitoneal lesions likely representing metastatic lymphadenopathy. Could mention that evaluation of bladder lesions with gallium-68 dotatate was limited by physiological tracer urinary excretion in this case (as mentioned below). Bladder paragangliomas do not usually demonstrate gallium-68 uptake. 24-hour urine collection demonstrated high normetanephrine levels of 24 umol/L. Collectively, these findings confirmed the diagnosis of polycythemia due to multiple urinary bladder paragangliomas.

**1.3. Conclusion:** Paragangliomas are associated with several genetic mutations in the literature. However, our patient had no identifiable mutations, indicating a possible alternative etiology. This article also highlights the importance of considering neoplasms in the differential diagnosis of hypertension in young patients. Fur-

ther, it is crucial to conduct clinical investigations on young hypertensive patients in order to exclude underlying causes.

**2. Introduction**

Polycythemia is a disorder defined as an increase in red blood cell mass, represented by increased hemoglobin and hematocrit levels [1]. The elevated red blood cell mass leads to increased blood viscosity associated with decreased blood flow and an increased risk of thrombotic events [1]. Clinical features include facial flushing, headaches, dizziness, erythromelalgia, and pruritus [2]. Polycythemia can be classified into primary and secondary causes. Primary causes of polycythemia include disorders such as polycythemia rubra vera (PRV) and familial/congenital polycythemia. Secondary causes of polycythemia include high altitude, chronic obstructive pulmonary disease, cyanotic heart disease, elevated carboxyhemoglobin, and conditions that cause low renal blood flow, such as renal artery stenosis and hydronephrosis [3]. Other secondary causes of erythrocytosis include hemoglobinopathies, erythropoietin (EPO) administration, and EPO-secreting tumors [3].

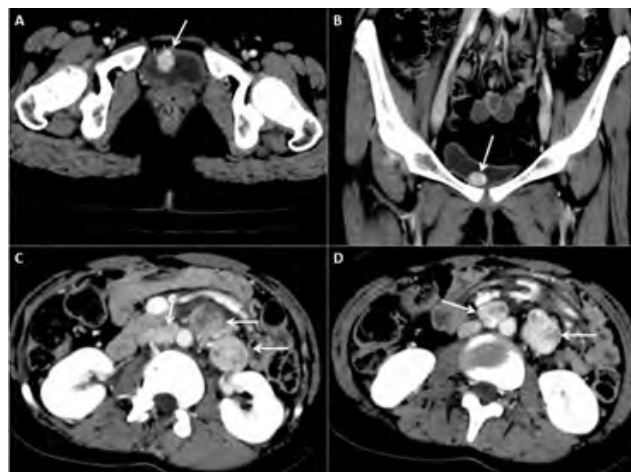
To arrive at a diagnosis of polycythemia, a comprehensive medical history, and appropriate diagnostic measures must be taken. The initial approach to diagnosis involves measuring serum EPO levels, which dictates further plans for evaluation [1]. Low EPO levels indicate primary polycythemia, and subsequent investigations should be geared towards detecting PRV. JAK2 V617F or exons 12 mutations are diagnostic for PRV and are positive in 97% of cases [4]. Measurement of serum ferritin and folic acid levels are also done, as low serum ferritin and folate levels are more associated with primary polycythemia [1]. High EPO levels indicate a secondary cause of polycythemia, and initial investigations include arterial oxygen saturation levels, Carboxyhemoglobin/methemoglobin levels, renal function tests, liver function tests, and abdominal ul-

trasound [5]. Further evaluations such as chest x-ray, lung function tests, bone marrow biopsy should be done when initial tests have not led to a diagnosis [1]. Paraganglioma-induced EPO-associated erythrocytosis is a rare occurrence, and there are only a limited number of reported cases in the literature. Therefore, we present the clinical description, as well as the radiological images, of a 14-year-old female presenting to the clinic with polycythemia due to multiple underlying paragangliomas.

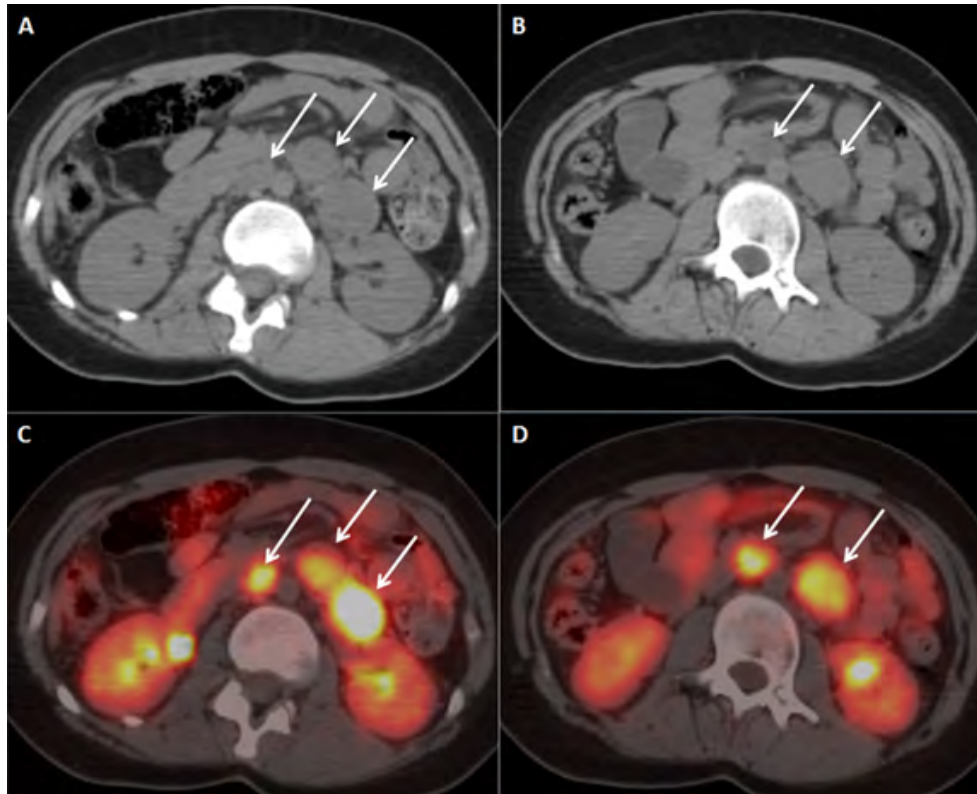
### 3. Case Report

A 14-year-old female presented to the clinic with sweating, palpitations, and palmar erythema. She was previously diagnosed with hypertension at age nine, for which secondary causes were not investigated. Her blood pressure was 200/100 mmHg, and her heart rate was 115 bpm on clinical examination. The patient's palmar surfaces were erythematic, and both hands were swollen. Laboratory investigations revealed an elevated hemoglobin level of 18.5g/dL, a low MCV of 69.0, and an elevated hematocrit of 57.5%. Moreover, the patient had normal levels of white blood cells and platelets. These clinical symptoms were attributed to the erythrocytosis; therefore, she was referred to hematology for work up. Further testing showed normal alanine transferase and creatinine levels. Genetic testing showed no mutations in the JAK2 V617F or exon 12, making the diagnosis of PRV unlikely. Serum EPO levels were obtained using standard immunoenzymatic assay methods and the level came at 36 mIU/mL (reference range between 4 and 21 mIU/mL). Given the elevated EPO level, a computed tomography (CT) of the abdomen was done and revealed (Figure 1) two intraluminal hyper-enhancing urinary bladder poly-

poid lesions; the largest is in the urinary bladder base (measured 2.0 x 1.5 cm), and the smaller one is in the dome (measured 0.5 cm). The lesions are confined to the urinary bladder wall with no extension to the perivesical fat. These findings are compatible with urinary bladder paragangliomas. The lesions are associated with multiple retroperitoneal heterogeneous hyper-enhancing solid lesions with low attenuation area suggesting cystic or necrotic components (largest lesion measured 3.3 x 2.5 cm). These retroperitoneal lesions likely represent metastatic lymphadenopathy from the urinary bladder paragangliomas, and a less likely differential diagnosis of additional paragangliomas. Whole body gallium-68 dotatate PET/CT scan (Figure 2) showed intense tracer uptake within the known necrotic retroperitoneal lymph nodes. No other size significant tracer avid lymphadenopathy identified elsewhere in the study. Assessment of the known bladder hypervascular lesions was limited by physiological tracer urinary excretion. Due to these incidental paraganglioma findings, 24 hours urine collection for normetanephrine was done and revealed a high level of 24.00umol/L. Whole exome sequencing was done looking for genetic alterations and was unremarkable. These findings confirm the diagnosis of polycythemia secondary to multiple paragangliomas with lymph node metastasis. Initial antihypertensive management included prazosin; however, the patient developed postural hypotension and was later prescribed phenoxybenzamine and labetalol. After discussing with a multidisciplinary tumor board and the patient?TURBT or cystectomy (partial or radical) was performed to excise paragangliomas. After following up with the patient, her hemoglobin and blood pressure levels returned to normal, and she reported relief of her symptoms.



**Figure 1:** Axial (A) and coronal (B) CT images of the pelvis from a portovenous phase of a contrast enhanced exam show a hyper-enhancing polypoid lesion arising from the urinary bladder wall (arrows). Axial (C and D) CT images from the same exam show multiple retroperitoneal heterogeneous hyper-enhancing solid lesions with low attenuation area suggesting cystic or necrotic components.



**Figure 2:** Axial non-enhanced CT images (A and B) and corresponding fused gallium-68 dotatate-fused CT/PET images (C and D) show intense tracer uptake within the retroperitoneal lesions/lymph nodes. Physiological tracer urinary excretion limits assessment of the bladder hyper-enhancing lesion.

#### 4. Discussion

In this article, we presented the case of a 14-year-old female with EPO-mediated erythrocytosis. She has been complaining of adrenergic symptoms that were attributed to the erythrocytosis. Upon referral to hematology, she was noted to have erythrocytosis with elevated EPO level. A search for EPO-producing masses revealed multiple paragangliomas. Indeed, paragangliomas are very rare, with a study reporting a prevalence of 0.1% in patients with sustained hypertension [2]. Patients with paragangliomas are often asymptomatic, and the masses are only discovered incidentally. In addition, given possible overlap in the symptoms and presentation of primary polycythemia and paraganglioma, some patient will attribute the sympathetic overdrive to polycythemia and may undergo therapeutic venesection to seek symptoms relief. However, symptoms of paragangliomas are a result of increased catecholamine secretion and include hypertensive urgency, sweating, headache, and pallor [2]. These are distinct from the hyperviscosity symptoms seen in patients with JAK2-positive PRV.

It is hypothesized that a gain-of-function HIF2A mutation in exon 12 may result in paraganglioma-associated erythrocytosis [6]. Precisely, all reports of such mutations influence the hydroxylation domain LxxLAP, leading to nuclear accretion of HIF2A and increased transcriptional activity of EPO [6-8]. These findings confirm the importance of the LxxLAP domain for stabilizing the HIF2A protein and controlling EPO, with upregulation leading to

erythrocytosis. Moreover, studies have found that 40% of paraganglioma patients have some form of genetic mutations, such as VHL, NF1, and RET mutations [9]. However, in the present case, whole genome sequencing revealed no mutations.

The initial diagnostic workup for suspected paragangliomas should include measuring blood or urine levels of catecholamines. If the analysis reveals increased levels, imaging is conducted using a CT or MRI scan [2]. While both have a very high sensitivity in diagnosing paragangliomas, studies have shown that MRI scans are superior with near 100% sensitivity [2]. Are you referring to I-123 MIBG scan? Perhaps you could comment on its utility (functional rather than diagnostic accuracy) for the diagnosis of paragangliomas. In this case, gallium-68 DOTATATE was performed instead (currently first line for diagnosis of paragangliomas). Could you comment in the body of this paper on the higher false negative rate of MIBG, how it would be less useful as compared to gallium-68 and its poor diagnostic accuracy. It would have been more useful in patients who are at risk of metastasis. Would I-123 MIBG have been useful in this case? Why was it not used? Recent studies have shown that complete resection of the paragangliomas is the only factor involved in a favorable outcome [10]. A recent article has reported that the prevalence of hypertension in children and adolescents is 3.5% [11]. Which study? Citation? In our patient, hypertension was initially not investigated and was later attributed to paragangliomas.

## 5. Conclusion

In this case report, we presented the case of a 14-year-old female with polycythemia and severe hypertension caused by multiple underlying paragangliomas. CT and in this case, its utility was limited due to physiological tracer excretion were utilized to reach the diagnosis successfully. Although paragangliomas are very rare, it is essential to consider this neoplasm as part of the differential diagnosis of hypertension in young patients. Moreover, we emphasize the importance of conducting clinical investigations for young hypertensive patients to exclude underlying causes.

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