Case Report

A case report of large bilateral pulmonary embolism in a patient with JAK2 positive mutation

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Abstract

Venous thromboembolism may be the primary presentation in patients with polycythemia Vera and essential thrombocythaemia and the incidence of venous thromboembolism increases with age [1]. The Janus kinase 2 (JAK2V617F) mutation is the main molecular marker of the Philadelphia-negative chronic myeloproliferative neoplasms, responsible for 95% of polycythemia; 50% of thrombocythemia Vera and myelofibrosis cases [2]. We report a case of 74 year-old-patient presenting with shortness of breath for 3 days. Past medical history (PMH) includes hypertension and previous basal cell carcinoma of the neck and nose for which patients had surgical reconstruction. The patient's vital showed oxygen saturation of 94% on 15 liters, tachycardia with heart rate >110, blood pressure 110/60 mmHg, and respiratory rate of 27. Laboratory results showed D-Dimer > 80000 ng/mL, Troponin T 130 ng/l, and Haemoglobin 182 g/L. Computerized tomography pulmonary angiogram showed bilateral pulmonary emboli with right heart strain. He was given a treatment dose of Tinzaparin and underwent emergency EkoSonic™ Endovascular System-Directed Thrombolysis (EKOS). The patient stabilized post EKOS and his vital signs improved within a few hours after the procedure. Oxygen saturation improved to over 96% on 2-3 liters and both tachycardia and tachypnoea improved. The patient has commenced on Apixaban 5 mg twice daily (BD). He tested positive for JAK2 mutation and met two major and one minor criterion for PV and was referred to Haematology for outpatient follow-up.

Introduction

Myeloproliferative neoplasms are uncommon disorders, and polycythemia vera (PV) is the most common myeloproliferative neoplasm with an annual incidence rate of 1–2/100 000 people [3]. PV is characterized by the presence of Janus kinase 2 (JAK2) mutation, erythrocytosis, and panmyelosis on bone marrow biopsy and is associated with an increased risk of thrombosis based on age and other risk factors. PV is commonly associated with venous thrombosis; however, few cases of PV associated with intracardiac thrombosis have been reported [4]. PV has also been reported to be associated with portal vein thrombosis eventually resulting in portal hypertension and liver cirrhosis [5].

Case presentation

We present a case of 74 year-old-patient who presented with sudden onset of shortness of breath for the last 3 days. PMH includes Hypertension (HTN) and resected basal cell carcinoma (BCC) on the nose and neck and underwent nasal reconstruction surgery. He was triple vaccinated against COVID-19. There was no recent travel history, and he denied any cough or fever. He had mild pleuritic chest pain and was visibly short of breath (sob) even at rest. Lab tests showed elevated D-Dimer, Troponin T, Haemoglobin, and N-terminal pro-brain natriuretic peptide (pro-BNP) as shown in Table 1. Vital signs were respiratory rate 27, Heart rate 110 bpm, oxygen saturation (SPO₂) 94% on 15 liters, and blood pressure 110/60 mmHg. On examination, the chest was clear, Heart sounds were normal, and the calves were soft and non-tender. There were no signs of deep venous thrombosis clinically. Computerized tomography scan of pulmonary angiogram showed bilateral large pulmonary embolism extending up to the main pulmonary artery, evidence of right ventricular strain, and right ventricle to left ventricle ratio (RV: LV ratio) 1.5. A bedside echocardiogram showed dilated right ventricle, but no left ventricular thrombus as shown in Figures 1,2. He received a stat dose of low molecular weight heparin (LMWH) of 12000 units. Pulmonary Embolism Severity Index (PESI) score was 124, which puts this patient in class 4 high-risk category with 30 days mortality up to 11.4% in this group. He underwent emergency EKOS in view of large pulmonary
A case report of large bilateral pulmonary embolism in a patient with JAK2 positive mutation and PV. He was reviewed by a Haematology consultant and was booked for outpatient follow-up. Clinical biomarkers improved and the patient was not requiring oxygen 48 hours post-procedure. He was discharged home on day 4 and a repeat echocardiogram before discharge showed improvement in the size of the RV.

Discussion

PV is a chronic myeloproliferative disease characterized and the diagnostic criteria used for its diagnosis include World Health Organisation (WHO) guidelines or British society for haematology (BCSH) guidelines. According to WHO criteria for women, all three major criteria (Hb > 16.0 g/dL or hematocrit > 48% or increased red cell mass; bone marrow biopsy showing panmyelosis and presence of JAK2 V617F or JAK2 exon 12 mutations) or the first two major criteria and minor criteria (e.g., subnormal serum erythropoietin level or presence of a clonal marker such as abnormal karyotype) are required for diagnosis. Table 1 summarizes the diagnostic criteria for PV and ET.

| Table 1: Lab test results trend. |
|----------------------------------|
| Investigation/Test               | Day 1 | Day 2 | Day 3 | Normal Value |
|----------------------------------|-------|-------|-------|--------------|
| Haemoglobin                      | 182   | 177   | 174   | 135-170 g/L  |
| White cell count                 | 10.48 | 10.83 | 8.22  | 3.5–11×10⁹/L |
| Neutrophils                      | 7.99  | 7.83  | 5.95  | 1.7-7.5×10⁹/L|
| Platelet                         | 145   | 166   | 187   | 150-400×10⁹/L|
| Mean cell volume                 | 94.1  | 95.0  | 96.8  | 79-92 fL     |
| Sodium                           | 136   | 134   | 138   | 135-145 mmol/L|
| Potassium                        | 3.7   | 3.4   | 3.7   | 3.5-5.1 mmol/L|
| Urea                             | 8.1   | 7.8   | 6.8   | 2.9 – 8.2 mmol/L|
| Creatinine                       | 90    | 77    | 73    | 66-112 umol/L|
| C Reactive Protein               | 72    | 85    | 87    | 0-5 mg/L     |
| Fibrinogen                       | 3.9   | 4.5   | 3.9   | 1.6-3.8 g/L  |
| Prothrombin time                 | 12.1  | 12.4  | 12.9  | 9-12 second  |
| Activated partial thromboplastin | 52.7  | 52.9  | 53.4  | 24.7-37 second|
| D-Dimer                          | > 80000| > 60000 | > 25000 | 0-400 ng/mL |
| JAK 2 mutation                   | -     | Positive | -     | -            |
| International Normalized Ratio   | 1.2   | 1.6   | 1.9   | 0.9-1.12 ratio|
| N-Terminal Pro brain natriuretic peptide | 7,136 | 3075 | 1456 | < 400 ng/L |

Table 2

| Polycythemia vera (PV) | Essential thrombocythemia (ET) |
|------------------------|-------------------------------|
| Major criteria         |                                |
| 1                      | Platelet count ≥ 450 × 10⁹/L  |
| BM biopsy shows hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) | BM biopsy shows proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyper lobulated nuclei. No significant left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers |
| 2                      | Not meeting WHO criteria for BCR-ABL1 + CML, PV, PMF, MDS, or other myeloid neoplasms |
| Presence of JAK2 or JAK2 exon 12 mutation | Presence of JAK2, CALR, or MPL mutation |
| Minor criteria          |                                |
| 1                      | Presence of a clonal marker (e.g., abnormal karyotype) or absence of evidence for reactive thrombocytosis |

Image 1: EkoSonic™ Endovascular System-Directed Thrombolysis (EKOS).

Image 2: Echo showing dilated RV 1.
the minor criterion of subnormal serum Erythropoietin (EPO) is necessary for the diagnosis to be made as shown in Table 2 [6]. It’s important to remember however that about 17% of patients may have normal EPO levels initially and hence may not fulfill the diagnostic criteria, however, the EPO levels drop on repeat testing thus fulfilling the diagnostic criteria [6]. This patient met two major criteria and one minor criterion as the patient had Hemoglobin > 180 g/dL, had JAK2 mutation, and subnormal erythropoietin level.

2016 World Health Organization diagnostic criteria for Polycythemia vera and essential thrombocythemia (Table adapted from Barbu, et al. Blood Cancer J, 2015; 5: e337 and Arber, et al. Blood. 2016; 127: 2391–2405).

Patients with MPNs have an increased risk of thrombotic events and these events increase the risk of mortality and morbidity in these patients. Both thromboembolism and cardiovascular complications are more prevalent in PV compared to other MPV disorders [7]. A retrospective study based on a total of 3001 PV patients reported that PV patients have a 3 and 13-fold higher risk of arterial thrombosis and venous thrombosis, respectively, compared with controls matched for age and sex at 3 months after initial diagnosis [8]. Thrombosis and Thromboembolism (TEs) are observed in approximately 39% - 41% of patients with PV and arterial thromboses comprise 60% - 70% of all cardiovascular events in patients with PV. Arterial thrombosis in these patients may present as a transient ischemic attack (TIA), cerebrovascular accident (CVA), acute myocardial infarction (AMI), and peripheral arterial occlusion [9].

The Gruppo Italiano Studio Policitemia study based on 1213 patients who were followed up for 20 years reported that approximately 64% of thromboembolic events occurred shortly before or at the time of diagnosis and the reported incidence is about 12% - 15% just before the diagnosis [10]. Similar findings were reported by the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study in which two-thirds of all events occurred shortly before or at the time of diagnosis [11].

There are few published case reports of elevated EPO levels associated with PV and Budd-Chiari syndrome (BCS) [4]. JAK2 mutation was reported to be associated with thromboembolism in a young patient without the myeloproliferative disorder in another case report [12]. JAK2 mutation sometimes can be falsely negative initially and in a case report of a 40-year-old patient with positive family history for DVT, developed thrombosis of the inferior vena cava extending to the suprahepatic veins and pulmonary arteries although, she tested negative for JAK 2 mutation initially but tested positive later [2].

PV can also be associated with intracardiac thrombus and a case report of a 60-year-old patient was found to have left apical thrombus after presenting with tinnitus and vertigo [3]. Several factors increase the risk of thrombosis in patients with PV including increased hematocrit, impaired fibrinolytic activity, platelet activation, leukocyte activation, endothelial damage, and increased whole-blood viscosity [3]. Key risk factors for intracardiac thrombus in these patients include valve disease, prosthetic valve, and cardiomyopathy [3,13].

Studies have shown that the key risk factors associated with recurrent thrombosis include old age, presence of cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, smoking, and previous thromboembolic events. A study of 494 patients reported that only age > 60 years and previous thromboembolic events were associated with a higher recurrence rate [14,15].

**Conclusion**

In conclusion, JAK 2 mutation PV is an uncommon condition but is frequently associated with venous thrombosis and has also been reported to cause intracardiac and portal vein thrombosis. EKOS is effective in short-term symptomatic relief of patients with large pulmonary embolism, but long-term benefits need further studies. These patients should be anticoagulated and have regular follow up with Haematology.

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