

# Neuropsychiatric Derangement by Polycythemia Vera: A Case Report of an Unexpected Disease Presentation and Review of the Literature

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## Keywords

Polycythemia vera · Neuropsychiatric symptoms · Psychosis · Chorea · Case report

## Abstract

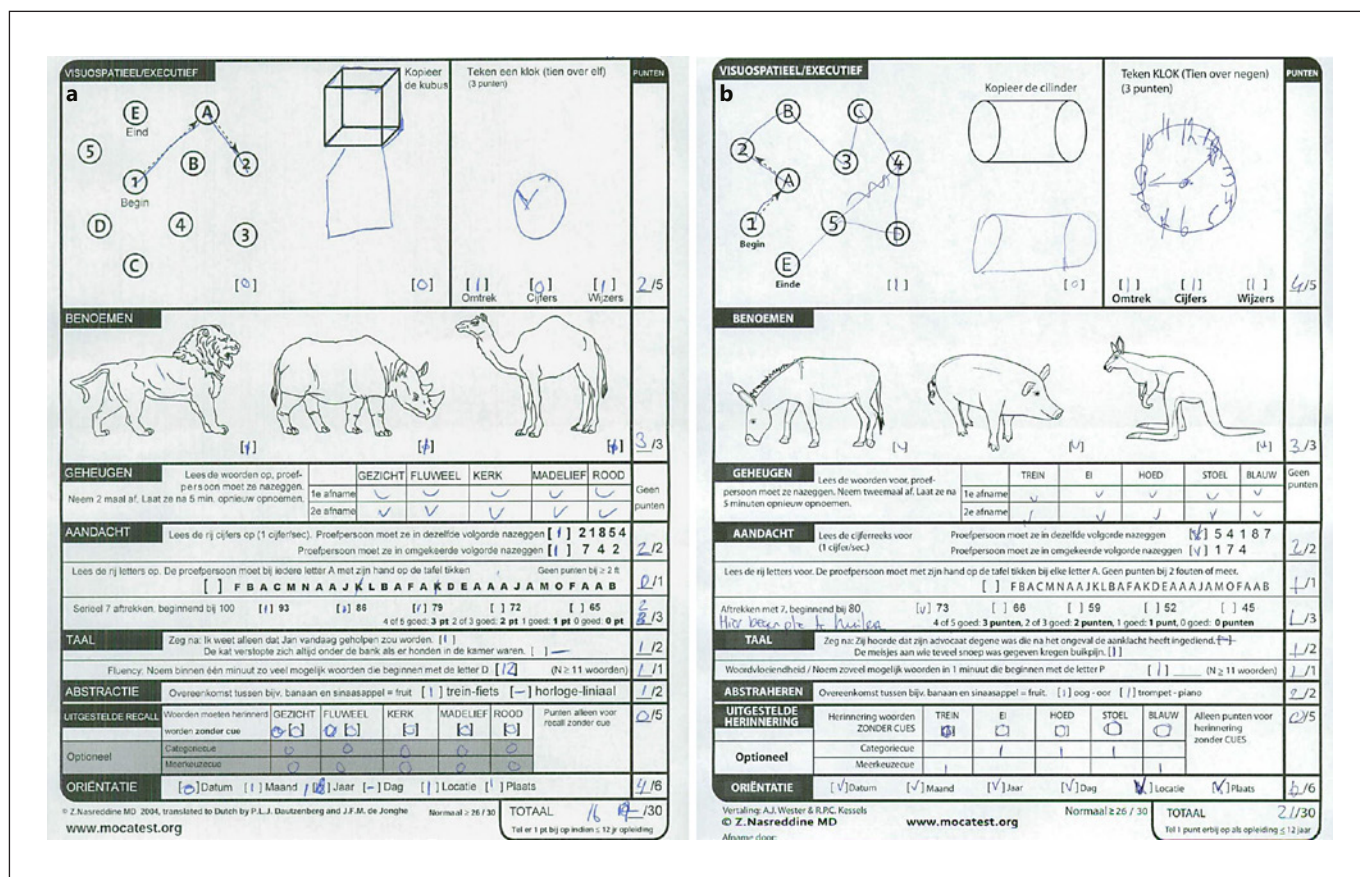
Cerebral infarction as well as other thromboses, headaches, and visual complaints are well-known symptoms of polycythemia vera. However, chorea and neuropsychiatric disturbances are less recognized consequences of this chronic disease. Whereas chorea is a rare but acknowledged symptom of polycythemia vera, neuropsychiatric symptoms have only sporadically been reported. We depict 2 patients with an unusual presentation of polycythemia vera. Our first patient presented with right-sided hemiballism and psychosis, and the second patient had a long diagnostic trajectory of unexplained chorea. In both cases diagnosis of JAK2 positive polycythemia vera was established, and in both cases remarkable recovery occurred after the initiation of phlebotomies. The underlying pathophysiology of these symptoms has not been clearly elucidated. Because of the unfamiliarity of the link between especially neuropsychiatric symptoms

and polycythemia, current reported numbers are probably an underestimation. Benefit of treatment appears to be large. We seek to create more awareness among physicians about this phenomenon.

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## Introduction

Polycythemia vera is a chronic myeloproliferative disorder of the bone marrow causing raised blood viscosity. The association between polycythemia and the increased risk of thrombosis is well-known [1, 2]. However, chorea and neuropsychiatric symptoms as utterance of the disease are less known. This can be a pitfall in diagnosis both for patients with unexplained neuropsychiatric symptoms if polycythemia is not considered as cause, as for those with polycythemia vera, if not explicitly asked for these complaints. We describe 2 cases in which these symptoms were the chief presenting symptom of polycythemia vera, with a delay in diagnosis and treatment as a consequence.



## Case 1

An 86-year-old lady was admitted to the geriatric ward because of subacute psychotic derangement and symptoms of aphasia, apraxia, and right-sided hemiballism. The hemiballism had been present for almost a year. It involved her right arm and leg but had not been a severe hinderance in her daily tasks and no treatment had been started. The psychotic symptoms were first noted a week before presentation, in midsummer during a heat wave. The psychotic derangement included delusions, preoccupation with certain words and the need to prove herself, a recurring theme in all of her stories. Since she had been completely independent at the age of 86 – even being a board member in one of her clubs – her changed mental state was especially concerning. She had no contributing medical history; and physical examination including a thorough neurological checkup revealed no further abnormalities. Laboratory workup showed a hemoglobin value of 16.1 g/dL, hematocrit value of 0.49 L/L, thrombocytes of  $605 \times 10^9/L$ , and leukocytes of  $12.9 \times 10^9/L$ . No evidence of microthrombi was found in the blood smear. No cause for a possible delirium was identified. A cerebral MRI scan showed mild generalized atrophy and signs of cerebral small vessel disease (Fazekas 2). There were no signs of recent infarction or

bleeding. Investigation of the cerebrospinal fluid showed no signs of an inflammatory process. There was a slightly increased tau protein and slightly decreased amyloid beta 42 protein in the cerebrospinal fluid, with a normal phospho-tau protein, not consistent with Alzheimer's pathology. During admission, a persistent pancytosis was seen, and therefore a primary hematological condition was considered. The erythropoietin level was low, and JAK2 V617F mutation was present in the peripheral blood. This was compatible with polycythemia vera. Phlebotomy was performed, after which the hematocrit level normalized, and also neuropsychiatric symptoms disappeared within 2 days. This is beautifully illustrated as a striking improvement in her performance on the Montreal Cognitive Assessment (shown in Fig. 1a, b). Carbasalate calcium was initiated and periodic phlebotomies were continued. The patient was discharged in a stable condition, and was able to resume her independent living situation. During hospital admission, no chemical cyto-reduction with hydroxycarbamide was commenced initially because of the possible neuropsychiatric side effects. However, since her clinical condition was stable after discharge, we prescribed hydroxycarbamide 4 weeks later. No neuropsychiatric symptoms reoccurred during 1-year follow-up.

**Table 1.** The WHO 2016 criteria of polycythemia vera

Diagnosis requires 3 major criteria or the first two major criteria plus the minor criteria <sup>a</sup>
<i>Major criteria</i>
Hemoglobin >16.5 g/dL or hematocrit >49% in males. Hemoglobin >16.0 g/dL or hematocrit >48% in females or increased red cell mass >25% above upper limit of normal
Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (different in size)
Presence of JAK2 V617F or JAK2 exon 12 mutation
<i>Minor criteria</i>
Subnormal serum erythropoietin level

WHO, World Health Organization. <sup>a</sup> Major criterion 2 may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentration >18.5 g/dL or hematocrit of >55.5% in males; hemoglobin concentration >16.5 g/dL or hematocrit of >49.5% in females), if major criterion 3 and the minor criteria are present.

## Case 2

A 71-year-old man was referred to the neurologist because of headaches, dizziness, double vision, and choreatic movements of the right arm. There had been a slight head trauma a few weeks earlier; however, the chorea was already present several months before the trauma. There was no relevant medical history. He felt like he had no control over his right arm and experienced trouble with daily tasks like cooking and writing. Neurological examination showed chorea of the right arm, as well as a Babinski reflex of the right foot; no other abnormalities were seen. A cerebral CT scan showed no evidence of subdural hematoma or an intracerebral mass. The symptoms progressed; and 6–8 weeks after initial presentation, a mildly progressive ataxia of the upper limbs was also noted. A cerebral MRI scan was performed, which showed a developmental venous anomaly in the insular region but no other abnormalities. At this point, laboratory tests for paraneoplastic antibodies, metabolic abnormalities, infectious serology, and DNA diagnostics for Huntington disease were performed but rendered no abnormalities. During the diagnostic trajectory, the patient experienced a syncope, for which he was referred to the cardiologist. No cardiac abnormalities were found and the syncope was explained as a vasovagal syncope. However, the cardiologist did a blood workup, which showed a markedly elevated hemoglobin value of 21.8 g/dL with a hematocrit value of 0.67 L/L. The leukocyte and thrombocyte count were  $7.3 \times 10^9/L$  and  $404 \times 10^9/L$ , respectively. No evidence of microthrombi was found in the blood smear. In retrospect, the laboratory results checked by the general practitioner 5 months earlier already showed a hemoglobin value of 22.2 g/dL. The patient was referred to the hematologist, JAK2 V617 mutation was confirmed in the peripheral blood, and the diagnosis of polycythemia vera was established. Phlebotomies and acetylsalicylic acid were initiated, after which the headache and visual disturbances recovered quickly. The chorea and ataxia showed slower but clear improvement. No hydroxycarbamide was started.

## Discussion

Polycythemia vera is a chronic myeloproliferative neoplasm which causes increased red blood cell production, independent of normal erythropoiesis regulation. Thrombocytosis and leukocytosis can coexist. The diagnostic criteria for polycythemia vera have been revised in 2016 by the World Health Organization and are shown in Table 1. In virtually all patients, a JAK2 V617F or JAK2 exon 12 mutation is present, which results in panmyelosis in the bone marrow. Classic symptoms are related to increased blood viscosity, with a major concern being arterial as well as venous thrombosis [1, 2]. Neurological manifestations such as headaches, dizziness, visual disturbances, paresthesias, and tinnitus are other well-known complaints, occurring in 50–78% of cases [1, 3]. However, chorea and neuropsychiatric disturbances, like in the cases we present, are less prevalent and much less recognized. These symptoms can be very incapacitating with an enormous impact on the patient and his or her environment. Especially in older patients, the differential diagnosis is broad, and a hematological disorder as a possible cause will often not be the first consideration of the treating clinician. The incidence of polycythemia vera increases with age, with an annual incidence range of 0.01–2.8 cases per 100,000 in Europe and North America. The median age at diagnosis is 60 years [1]. Therefore, it is not unlikely to encounter a patient with the disease in your daily practice. In both patients described above, the start of treatment with lowering of hemoglobin and hemato-

**Table 2.** Overview of all descriptions of cases with neuropsychiatric symptoms in polycythemia vera found in the literature

Author, year	Gender and age	Symptoms	Hemoglobin/hematocrit*	Used therapies (chronological)	Effects
Murray et al. [13], 1991	Male, 72	Eleven years after polycythemia vera diagnosis Depression, suicidal ideation Transient ischemic attacks Auditory hallucinations, paranoid delusions, and disorientation	Unknown	Haloperidol and electroconvulsive therapy Lofepramine Electroconvulsive therapy and fluoxetine Busulfan and pentoxifylline	Initially: good recovery. Relapse after 3 weeks No effect Patient remained well after 6 weeks, residual anxiety symptoms No effect on depression
Mazzoli et al. [14], 1992	Female, 69	Initial symptoms: myocardial infarction and stroke which led to polycythemia vera diagnosis Nine years after polycythemia vera diagnosis Depression, suicidal ideation Delusions	RBC 9.9 million/mm <sup>3</sup> Hb and Ht: unknown		Subjective: mental status returned to normal, cognitively intact Objective: abbreviated mental test score: 10/10
Chawla et al. [15], 1993	Female, 65	No prior diagnosis of polycythemia vera Patient was found wandering on the streets; incoherent speech, inappropriate behavior, and visual hallucinations Neuropsychological testing: information/orientation scale of the Clifton assessment procedures for the elderly: 0/12	Hb 18.9 g/dL, Ht 0.56 L/L	Phlebotomy	
Di Pollina et al. [17], 2000	Male, 76	No prior diagnosis of polycythemia vera Confusion, psychomotor slowing, abulia, problems driving, difficulties in concentrating Neuropsychological testing: revealed severe deficits in executive function, mildly impaired memory	Hb 19.2 g/dL, Ht 0.60 L/L	Phlebotomy (3 occasions) and hydroxycarbamide	Subjective: functional and cognitive improvement, no further confusional episodes Objective: neuropsychological testing showed normalization in constructional praxis, reasoning and calculation. Moderate to severe deficits in executive function persisted and memory was unchanged
Alkemade et al. [18], 2008	Female, 67	No prior diagnosis of polycythemia vera Rapid progressive cognitive impairment, memory loss, inability to perform activities of daily living Balance difficulties	Hb 22.05 g/dL, Ht unknown	Phlebotomy and acetylcysteine 100 mg once daily	After 6 weeks, global cognitive and executive functions improved and the patient was able to perform daily tasks at a reasonable level, yet not on preexisting level Subjective: after fourth phlebotomy, feeling better and chorea attacks disappeared
Severs et al. [19], 2012	Female, 73	No prior diagnosis of polycythemia vera Involuntary movements of arms and head, numbness in left upper quadrant of the face, inability to speak Progressive behavioral change, e.g., social distancing, unrestrained verbal comments	Hb 18.7 g/dL, Ht 0.57 L/L	Phlebotomy, 500 mL twice a week	Objective: neuropsychological testing revealed significant improvement in frontal characteristics No effect Subjective decrease of involuntary movements
Garcia et al. [20], 2018	Male, 96	Treated for polycythemia vera with hydroxycarbamide for a long time. However, the hematologist had decided to stop treatment one month prior of presentation Sudden onset in left-sided chorea of the upper limb and face Progressive behavioral change, e.g., disinhibition, inappropriate verbal comments, and unrestrained laugh	Hb 15.5 g/dL, Ht 0.46 L/L	Haloperidol and clonazepam Hydroxycarbamide	

The article of Fones et al. [16] was not available in full text. \* At the moment of presentation with neuropsychiatric symptoms.

crit levels resulted in a clear improvement of presenting symptoms. The first case shows us that the absolute hemoglobin values do not have to be extremely elevated to cause symptomatology, which could be an extra reason why polycythemia is overlooked as a possible cause. In the first case, diagnostic delay was only a couple of weeks, but in the second case it was 5 months, and correct diagnosis was preceded by comprehensive alternative diagnostic tests. We therefore think it is very important to bring the possible relation of atypical neurological and neuropsychiatric symptoms and polycythemia vera to the attention.

Chorea has been described as a feature of polycythemia vera in the international literature since 1909 [4]. Until 1972, only 9 cases had been reported, with Ashenhurst in 1972 being the first to report a male patient [5]. In the following years, reports increased. Chorea appears to affect 1–2.5% of polycythemic patients, with a predominance for females in a 5:2 ratio [6]. It usually seems to improve when the polycythemia is corrected; however, it can also improve spontaneously, and in rare cases appear to persist in spite of treatment. It is often bilateral but can also occur one-sided [5–9]. Remarkably, in both cases, the chorea was unilateral. The underlying pathophysiology has not been well understood. It is hypothesized to be based on hyperviscosity leading to a sluggish cerebral blood flow, venous stasis, and impaired tissular oxygen/glucose metabolism; predominantly in the basal ganglia, rendering them more vulnerable to toxins and metabolic factors. However, this has not been uniformly confirmed with imaging studies [10, 11]. Possibly, the signs of small vessel disease on the MRI scan in patient 1 were compatible with the long-term sluggish blood flow due to polycythemia. Additionally, dopaminergic hyperactivity can be enhanced by receptor hypersensitivity in a setting of reduced catecholamine levels in the elderly patient, estrogen-deficit-induced dopamine receptor hypersensitivity in postmenopausal women and possibly by dopamine excess due to platelet congestion in the cerebral vasculature [6, 7, 12].

Whereas, chorea is a rare but recognized symptom of polycythemia vera, neuropsychiatric symptoms have only been reported in 8 former published reports (shown in Table 2) [13–20]. The first reports describing psychiatric symptoms date from the early nineties, in which 3 patients were admitted with acute mania or depression [13–15]. Two of them had been diagnosed with polycythemia vera several years before presentation and in 1 patient it was discovered during admission. Remarkably, all patients had transient ischemic attacks in their medical his-

tory. Despite poststroke depression being a rather well-known phenomenon, 2 of these patients had their first episode many years after the reported minor strokes; therefore, secondary mood disorder was considered less likely by their treating physicians [13, 14]. Moreover, in 2 cases, the mood disorder completely normalized after phlebotomy and normalization of the hemoglobin levels, which supports the possible causality between polycythemia vera and the occurrence of these mood disorders [13, 15]. Between 2000 and 2019, only 5 more cases with neuropsychiatric symptoms have been published. All these patients presented with cognitive impairment including confusion, psychomotor slowing, general behavioral changes, and frontal lobe syndrome. One of the patients, like the first case we presented, even met the criteria for clinical dementia [16–20]. It is promising that each of these reports has shown at least partial, subjective reversibility of the cognitive deficits. In addition, in our case as well as the patient with frontal lobe syndrome described by Severs et al. [19] in 2012, neuropsychological testing showed significant improvement after polycythemia vera treatment.

Interestingly, the patients portrayed in these studies presented with hemoglobin levels varying between 15.5 and 22.1 g/dL, which as mentioned earlier, shows us that the absolute hemoglobin values do not have to be extremely elevated to cause symptomatology; possibly leading to an underestimation of polycythemic-induced cognitive impairment. Therefore, creating awareness among physicians is even more important, since the literature on this topic is scarce.

The optimal treatment for neuropsychiatric disturbances related to polycythemia vera seems to be optimal reduction of hematocrit levels. It appears reasonable to follow the same treatment algorithms as for polycythemia vera in general to reach this goal. In current Dutch and European treatment guidelines, hydroxycarbamide and pegylated interferon alfa-2a are suggested as first-line treatment options, with some room for the first-line treatment with Busulfan in elderly patients in the European LeukemiaNet guidelines [21–23]. Pegylated interferon alfa-2a does not seem prudent in these cases because of its possible side effects of psychiatric symptoms and tremor. Busulfan could have been a valuable treatment option in our 2 patients but is not registered as a first-line treatment regimen in The Netherlands. In younger patients, busulfan is discouraged because of its carcinogenic potential.

## Conclusion

Cerebral infarction, headache, and visual disturbances are well-known complications of polycythemia vera, whereas chorea and neuropsychiatric disturbances are a rare but incapacitating consequence. It is important to consider the diagnosis of a myeloproliferative disorder in case of persistent pancytosis. Symptoms can be very incapacitating but often be reversed with phlebotomy. It could be advised that in cases of unexplained neuropsychiatric disease, polycythemia vera should be considered by performing a blood count; and in cases of polycythemia vera, neuropsychiatric symptoms should be evaluated by the physician.

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## References

- 1 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. *WHO classification of tumours of haematopoietic and lymphoid tissues*. 4th ed.; 2017.
- 2 Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2019 Jan;94(1):133–43.
- 3 Silverstein A, Gilbert H, Wasserman LR. Neurologic complications of polycythemia. *Ann Intern Med*. 1962;57:909–16.
- 4 Bordachzi P. Choreia und polycythemia vera. *Prag Med Wochr*. 1909;34:253.
- 5 Ashenhurst EM. Choreia complicating polycythemia rubra vera. *Can Med Assoc J*. 1972 Sep 9;107(5):434.
- 6 Bruyn GW, Padberg G. Choreia and polycythemia. *Eur Neurol*. 1984;23(1):26–33.
- 7 Janavs JL, Aminoff MJ. Dystonia and chorea in acquired systemic disorders. *J Neurol Neurosurg Psychiatry*. 1998;65:436–45.
- 8 Coppack SW, Gibberd FB. Choreia with transitional myeloproliferative disease. *J R Soc Med*. 1985 Oct;78(10):864–6.
- 9 Nazabal ER, Lopez JM, Perez PA, Del Corral PR. Choreia disclosing deterioration of polycythemia vera. *Postgrad Med J*. 2000 Oct;76(900):658–9.
- 10 Thomas DJ, du Boulay GH, Marshall J, Pearson TC, Ross Russell RW, Symon L, et al. Cerebral blood-flow in polycythemia. *Lancet*. 1977 Jul 23;2(8030):161–3.
- 11 Kim W, Kim JS, Lee KS, Kim YI, Park CW, Chung YA. No evidence of perfusion abnormalities in the basal ganglia of a patient with generalized chorea-ballism and polycythemia vera: analysis using subtraction SPECT co-registered to MRI. *Neurol Sci*. 2008 Oct;29(5):351–4.
- 12 Marvi MM, Lew MF. Polycythemia and chorea. *Handb Clin Neurol*. 2011;100:271–6.
- 13 Murray D, Hodgson R. Polycythemia rubra vera, cerebral ischaemia and depression. *Br J Psychiatry*. 1991;158:842–4.
- 14 Mazzoli M, Benazzi F. Polycythemia and psychotic depression. *Br J Psychiatry*. 1992;160:134–5.
- 15 Chawla M, Lindsay J. Polycythemia, delirium and mania. *Br J Psychiatry*. 1993;162:833–5.
- 16 Fones C, Tsoi WF. Polycythemia rubra vera presenting with depression: recognising the syndrome abulia. *Br J Clin Pract*. 1995;49(2):97–9.
- 17 Di Pollina L, Mulligan R, Juillerat van der Linden A, Michel JP, Gold G. Cognitive impairment in polycythemia vera: partial reversibility upon lowering of the hematocrit. *Eur Neurol*. 2000;44(1):57–9.
- 18 Alkemade GM, Willems JM. Polycythemia vera presenting as sudden-onset cognitive impairment. *J Am Geriatr Soc*. 2008;56(12):2362–3.
- 19 Severs M, Boelens HM, Diraoui SB, Schuur J. Choreia and a frontal lobe syndrome: a rare neurological presentation of polycythemia vera; a case report. *J Am Geriatr Soc*. 2012;60(3):589–90.
- 20 Garcia-cabo C, Fernandez-dominguez J, Mateos V. Sudden hemichorea and frontal lobe syndrome: a rare presentation of unbalanced polycythemia vera. *BMJ Case Rep*. 2018;2018:bcr2017223867.
- 21 HOVON werkgroep CML/MPN. Polycythemia Vera (PV) 2018; Autorisation date 9th of January 2018.
- 22 Barbui T, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European leukemianet. *J Clin Oncol*. 2011 Feb 20;29(6):761–70.
- 23 Vannucchi AM, Barbui T, Cervantes F, Harrison C, Kiladjan J, Kröger N, et al. Buske C on behalf of the ESMO guidelines committee. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2015;26(Suppl 5):v85–v99.

## Statement of Ethics

Written informed consent for publication was obtained from the patient for publication of this case report and accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Heleen De Lil: extraction of data from the patient file and construction of the manuscript. Michelle van Beek: construction of the manuscript (specifically the literature study on neuropsychiatric symptoms in polycythemia vera). Alexandra Herbers: extraction of data from the patient file and critical revision of and additions to content of the manuscript. Ellen van der Holst: critical revision of and additions to content of the manuscript. Karen Keijsers: extraction of data from the patient file and critical revision of and additions to content of the manuscript.