Rare disease

Cerebral infarction due to smoker's polycythemia

Kiran Teresa Thakur,¹ M Brandon Westover²¹Massachusetts General Hospital, Department of Neurology, Boston, Massachusetts, United States;²Partners (Brigham & Women's Hospital/Massachusetts General Hospital), Department of Neurology, Boston, Massachusetts, United States

Correspondence to Dr M Brandon Westover, mwestover@partners.org

Summary

A 65-year-old man presented with fluctuating focal neurological deficits and neuroimaging findings of multiple small cerebral infarctions. His medical investigation revealed a >100 pack/year smoking history, and a haematocrit >60. Subsequent investigations led to a diagnosis of cerebral infarction due to smoker's polycythemia, the third such case reported in the medical literature. The patient's neurological deficits resolved completely with subsequent haematocrit reduction. This brief report reviews the differential diagnosis of polycythemia, current knowledge of the mechanisms by which smoker's polycythemia may lead to ischemic stroke, and recommendations for management.

BACKGROUND

Smoking is well known risk factor for ischaemic stroke via its role in promoting cardiovascular disease. However, smoking as a cause of hyperviscosity leading to stroke is much less well known. Smokers' polycythemia is defined by a high plasma red blood cell (RBC) concentration due to increased RBC count and decreased plasma volume, attributable to chronic tobacco smoking.¹ In contrast to the better known disorder of polycythemia vera, cerebral infarction has rarely been reported as a complication of smokers' polycythemia.² We report a case of cerebral thrombosis due to smokers' polycythemia, the third such case reported in the literature, and review current concepts relating to pathophysiology and management.

CASE PRESENTATION

A 65-year-old Caucasian man presented with fluctuating right-sided weakness. When he awoke in the morning, he had difficulty fastening the buttons of his shirt and tying shoes with his right hand and he was unable to stand because of right leg weakness. In the emergency department, he had right facial droop, dysarthria and flaccid paralysis of the right arm and leg with normal vital signs. Medical history was remarkable only for having smoked at least two packs of cigarettes daily for 50 years.

INVESTIGATIONS

On presentation, brain MRI showed several small foci of decreased diffusion in the left thalamocapsular junction, left posterior putamen and left corona radiata, without associated T2/fluid attenuated inversion recovery (FLAIR) signal abnormalities, together considered suggestive of acute infarction. Small T2/FLAIR abnormalities suggestive of remote infarction were also seen in the right external capsule and genu of the internal capsule. The major intracranial flow voids were patent. His haematocrit was 60.9% with haemoglobin concentration of 21 g/dl. Counts for white blood cells and platelets were normal. Erythropoietin levels were normal and primary polycythemia vera was ultimately excluded with negative genetic testing for the JAK2 mutation.³

DIFFERENTIAL DIAGNOSIS

Polycythemia is defined by elevated plasma red cell concentrations, with haemoglobin and haematocrit values exceeding 16.5 g/dl and 48% respectively, for women; or 18.5 g/dl and 52 for men. The differential diagnosis of polycythemia can be organised as follows. Polycythemia is classified as 'absolute', due to increased RBC production, or 'relative', due to decreased plasma volume (table 1). Absolute polycythemia is further classified as primary when increased RBC production occurs independently of erythropoietin levels (eg, as in polycythemia vera). Secondary polycythemia vera occurs when RBC production is induced by increased levels of circulating erythropoietin (eg, as in hypoxic states such as chronic obstructive pulmonary disease (COPD) or cyanotic heart disease, or due to erythropoietin-secreting tumours).

TREATMENT

The patient was treated with aspirin and administration of intravenous normal saline. For the first 12 h of hospitalisation, his examination findings fluctuated four times between flaccid right hemiplegia and complete resolution of weakness. However, after 12 h of treatment, his

Table 1 Differential diagnosis and classification of polycythemia

Genetic mutations (absolute, primary)

–Polycythemia vera (JAK2 mutation), high oxygen affinity haemoglobins, erythropoietin receptor mutations

Erythropoietin-producing cancers (absolute-secondary):

–Renal cell carcinoma, hepatocellular carcinoma, haemangioblastoma, uterine fibroids

'Appropriate' ↑ in erythropoietin (absolute-secondary)

–COPD, right-to-left cardiac shunts, obstructive sleep apnea, high altitude, red cell defects, CO poisoning (including chronic, due to smoking), cobalt poisoning

Miscellaneous causes (absolute-secondary)

–Androgens/anabolic steroids, blood doping, exogenous erythropoietin...

Low plasma volume (relative)

–Caffeine, diuretics, smoking, CO poisoning...

Combined (relative and absolute-secondary)

–Smokers' polycythemia

Figure 1 The relationship between carbon monoxide levels and neurological damage and stroke.

deficits resolved completely and did not return, coincident with a reduction of the haematocrit to 51%. This led us to hypothesise that his fluctuating motor deficits were due to changes in his high viscosity state, leading to multiple episodes of reversible cerebral small-vessel occlusion.

OUTCOME AND FOLLOW-UP

The patient was discharged with no neurological deficits and a final diagnosis of ischaemic stroke due to smoker's polycythemia.^{1 2} He was counselled to quit smoking.

DISCUSSION

Smokers' polycythemia is a 'mixture' of relative polycythemia, due to decreased plasma volume, in combination with secondary polycythemia, due to chronic carbon monoxide (CO) exposure from tobacco smoke.^{1 4} The mechanisms underlying stroke in smokers' polycythemia are most likely a combination of vaso-occlusive events due to increased blood viscosity as well as processes involved in chronic CO poisoning (figure 1). In particular, CO causes at least three neurologically harmful effects. First, it binds haemoglobin with a higher affinity than oxygen, causing a left-shift of the carboxyhaemoglobin dissociation curve, leading in turn to hypoxemia. Second, CO causes local mitochondrial dysfunction which, combined with hypoxemia, leads to local tissue hypoxia, preferentially affecting the most metabolically active neural structures. Third, CO exposure leads to decreased plasma volume. The mechanism underlying this effect is not known with certainty, though there is some evidence to suggest that it may occur via CO causing leakage of albumin in renal glomeruli. In any case, decreased plasma volume increases haematocrit, inducing a relative polycythemia. On the other hand, hypoxemia serves as a signal triggering the production of erythropoietin, which activates a compensatory increase in RBC production, further increasing the haematocrit and inducing absolute polycythemia. Finally, blood viscosity increases with haematocrit, ultimately placing the

patient at risk for local thrombosis and resulting hypoxic-ischaemic stroke.

The relationship between blood viscosity and haematocrit is non-linear, such that at higher haematocrit values, a further small increase results in a disproportionately large jump in blood viscosity.⁵ This results in a theoretical 'threshold effect', such that beyond a certain value the risk of vaso-occlusive events rapidly rises. Early clinical evidence for this concept led to recommendations to maintain the haematocrit in patients with polycythemia vera <45% in males and <42% in females, largely by means of phlebotomy.^{6 7} This practice remains standard care for treating polycythemia vera,^{3 8} though a recent prospective clinical trial failed to demonstrate increased risk of thrombotic events with haematocrit values up to 55%, leaving the optimal haematocrit target in doubt.^{8 9} Our patient had a heavy smoking history, and was found to have elevated viscosity of his serum at the time he presented. With aggressive fluid hydration, and a subsequent decline in his haematocrit, our patient's symptoms resolved supporting our hypothesis that hyperviscosity was responsible for his deficits.

The target haematocrit is even less clear in cases of smokers' polycythemia, because, on theoretical grounds, erythrocytosis in this situation represents to a certain extent an 'appropriate' physiological response to hypoxemia. Thus, whatever the ideal haematocrit in cases of primary polycythemia, the corresponding ideal in smokers' polycythemia is likely to be higher. For this reason, no consensus exists regarding target haematocrit levels in smokers' polycythemia, and the role of phlebotomy is consequently unclear. Our patient's symptoms fluctuated prior to intravenous fluids and aspirin then fully resolved when the haematocrit dropped by 10 points to 51. General recommendations typically include low-dose aspirin, volume resuscitation and smoking cessation measures. In our case and in the two previously reported cases of stroke due to smokers' polycythemia, there were no reported recurrences of stroke. Further investigations are needed to clarify the optimal management strategy.

Learning points

- ▶ Smoking is a well-described cause of polycythemia, though reported only twice before as a cause of ischemic stroke.
- ▶ Smoker's polycythemia is a 'mixed' type of polycythemia, due to a combination of decreased plasma volume and increased RBC production, attributed to chronic CO exposure present in inhaled cigarette smoke.
- ▶ Chronic CO exposure is hypothesised to cause cerebral infarction via a combination of increased blood viscosity (due to increased RBC volume and decreased plasma volume), hypoxemia, and local tissue hypoxia.
- ▶ The 'target' haematocrit in symptomatic smoker's polycythemia is unknown, though theoretical considerations suggest that target values in secondary smoker's polycythemia and other secondary polycythemias may be higher than currently recommended targets in primary polycythemia. The role of phlebotomy in smoker's polycythemia, if any, is unknown.
- ▶ Reasonable management recommendations in symptomatic smoker's polycythemia (such as cases of cerebral infarction) include aggressive hydration measures (eg, intravenous fluids) aimed at lowering haematocrit values and blood viscosity, low-dose aspirin therapy and smoking cessation.

Competing interests None.

Patient consent Obtained.

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