A rare case: Mania associated with pazopanib

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Abstract
Mania typically presents with a well-denoted period of abnormal and persistently elevated or irritable mood, and increased activity or energy almost daily for at least a week. This mood disturbance is usually functionally dilapidating in aspects of social or occupational functioning, sometimes even requiring hospitalisation to prevent harm to self or others. We report an interesting case of first presentation of mania in a 61-year-old female with ongoing metastatic sarcoma, with a potential association with a chemotherapy drug – pazopanib.

Keywords
Mania, sarcoma, pazopanib

Introduction
Manic episodes are classified in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) under bipolar and related disorders. Mania is characterised by a period of abnormally persistent elevated and expansive mood, with increased activity or energy. This lasts for at least a week and is present for the majority of the day, almost every day of the week. The DSM-V criteria include inflated self-esteem, reduced need for sleep, increased talkativeness, racing thoughts, distractibility, increased activity (goal or non-goal directed) and unrestrained involvement in activities with potentially regrettable consequences. At least three of the mentioned symptoms are necessary for diagnosis, and this mood disturbance has to be sufficiently severe enough to cause significant impairment in social functioning to require hospitalisation.

The lifetime prevalence of mania is estimated to be 0.6%, with the first manic episode presenting at a mean of 18 years of age. Nearly all (95%) bipolar individuals have their first manic episode before the age of 26. However, given that there is a constant and stable increase in life expectancy secondary to health-care improvements, we would also expect an increase in older adults diagnosed with bipolar disorder. Late-life mania in those aged >50 was observed to have an estimated prevalence of 6.0%.

Management of acute mania is aimed at alleviating symptoms in order to attempt restoration of baseline psychosocial functioning. This involves controlling the symptoms of agitation and impulsivity to ensure the safety of patients and those around them. Traditionally, the mainstay for treatment of acute mania includes lithium, anti-convulsants such as valproate, typical or atypical anti-psychotics and benzodiazepines.

Pazopanib is a tyrosine multikinase inhibitor that is currently licensed for use in treatment of advanced renal-cell carcinomas and soft-tissue sarcomas. It limits tumour growth via inhibition of intracellular tyrosine kinase pathways of vascular endothelial growth factor receptors (VEGFR-1,2,3), platelet-derived growth factor receptors (PDGFR-alpha and beta), fibroblast growth factor receptors (FGFR-1,3) and many others.

We report an interesting case of possible pazopanib-induced mania in a 61-year-old Chinese female with ongoing metastatic high-grade sarcoma.

Case report
In January 2020, our patient presented with shortness of breath associated with wheezing. A chest radiograph picked up pulmonary nodules, but the patient refused further investigations. The only past medical history of note was poorly controlled hypertension.
Subsequently, she re-presented in July 2020 for persistent right upper-limb and neck pain, along with the ongoing wheeze which had not resolved from the previous presentation. She eventually underwent a computed tomography (CT)-guided biopsy of the lung nodules in question, and was diagnosed with metastatic undifferentiated sarcoma, likely leiomyosarcoma of a uterine primary. Sites of disease included the uterus, lungs, liver, adrenals, kidneys, thyroid and bones, with bulky high cervical-spine metastasis.

She underwent radiotherapy for her cervical-spine metastasis in August 2020 and was given three cycles of doxorubicin in September 2020. Unfortunately, there was disease progression. Pazopanib was then trialled in November 2020. Subjectively, the patient reported that her right upper-limb and neck pain improved significantly after commencement of pazopanib.

In December 2020, she presented to the emergency department with an episode of non-vertiginous giddiness, which resulted in a near-fall incident. She also reported a loss of appetite one week prior. Interestingly, her family reported that she had become more talkative three weeks after commencement of pazopanib. Her oncology team noted that she had demonstrated symptoms of mania during admission – decreased need for sleep, pressured speech, flight of ideas and distractibility during conversations. Hence, she was referred to psychiatry for a subacute behavioural change involving manic features for someone with no background psychiatric illness.

During multiple interviews, the patient expressed various grandiose claims such as being the CEO/CFO of different companies, meeting presidents of many countries and having various university degrees, the majority of which were corroborated with her family to be untrue. Throughout her early admission, the patient reported an elevated mood and that she was in hospital to play mobile games rather than for treatment. Nurses reported irritability when demands were not met, and the patient would only sleep two to three hours per night and would constantly be talking to herself. Assessment of her mental state by the different teams revealed flight of ideas, pressured speech and distractibility on engagement, without any obvious signs of delirium.

Conversely, she reported poor appetite and attributed this to her medications. The patient also revealed that she had spent large sums of money on mobile games over the past couple of years. However, this was in keeping with her pre-morbid spending habits as corroborated by the family.

Faced with a diagnostic challenge, the differentials at this stage for the subacute mood and behavioural change were further progression of the patient’s metastatic disease with spread to the brain or a late-onset first presentation of a primary psychiatric illness of mania.

A thorough battery of investigations were done to explore potential organic causes for this subacute change in mental state. Blood investigations came back largely normal. A CT scan of the brain showed a faint hypodensity in the right parieto-occipital region that was non-specific, possibly representing a small infarct; there was no evidence of intracranial metastatic disease, territorial infarct or intracranial haemorrhage. Histopathology samples and viral assays returned negative results from a lumbar puncture. A magnetic resonance imaging (MRI) scan of the brain described the small artefact as indeterminate for a small peripheral acute infarct with petechial haemorrhage in the right parasagittal parietal lobe or metastasis. Neurology was consulted, and they commented that the lesion was unlikely to have caused the mood and behavioural changes. They further suggested a follow-up scan to monitor the lesion. The MRI scan of the brain was repeated two weeks later, showing the same non-enhancing cortical lesions as indeterminate for evolving infarcts or treated metastases.

From the corroborative history given by the family that the patient had small elevations in mood and hastening of speech after three weeks of receiving pazopanib, our pharmaceutical colleagues were consulted. PubMed searches found that neuropsychiatric side effects with pazopanib were indeed very rare. However, the decision to withhold pazopanib was made early in the admission.

Treatment was initially aimed at rapidly attenuating the manic symptoms with the atypical anti-psychotic, olanzapine. The patient was initially non-compliant with medication but was eventually amenable after coaxing. Dosage was started at 2.5 mg once at night with a top up of 2.5 mg for breakthrough agitation. This was increased over a week to 10 mg b.i.d. Furthermore, benzodiazepines were added on halfway for their sedative, relaxant and anxiolytic properties, initially starting with 0.5 mg lorazepam b.i.d. and switching it out for 5 mg of longer-acting diazepam b.i.d. The patient’s mental state gradually improved after a week of medication. Thought process gained relevance and order, whilst speech was no longer pressured; the patient’s sleep cycle also started to normalise. Figure 1 denotes the timeline from initiation of pazopanib with onset of manic symptoms through to resolution of symptoms.

![Figure 1. Flowchart showing timeline from initiation of pazopanib, with onset of manic symptoms, through to resolution of symptoms.](image-url)
The patient was eventually discharged, and plans were made to follow up with her in the outpatient setting. A collective decision was eventually made to opt for expectant management with repeated scans while continuing to hold off pazopanib. Unfortunately, a subsequent MRI brain scan in February 2021 showed interval development of seven rim-enhancing focal lesions in both the cerebral and cerebellar hemispheres, which likely represented haemorrhagic metastases. Despite progression of the disease, the patient did not re-present with any manic symptoms, and a decision to continue withholding pazopanib was also made.

Discussion

Using the Naranjo Scale, the emergent manic symptoms that this patient experienced scored a 2, indicating it as a possible adverse drug reaction of pazopanib.

Neuropsychiatric symptoms in pazopanib therapy are very rare, with only a single case summary reported. In this particular case report, hallucinations were experienced by a 47-year-old male after initiation with pazopanib. The patient was negative for cranial metastasis on radiography and had no history of steroid use. Pazopanib was initially stopped, with recovery of symptoms. Upon rechallenge, the hallucinations recurred. The decision to discontinue fully was made, and the patient did not re-present with any further hallucinations.7

Other tyrosine kinase inhibitors which have seen more extensive and longer use have brought up limited case reports. Neuropsychiatric symptoms such as cognitive impairment, memory deterioration and hallucinations were observed in a number of patients undergoing tyrosine kinase inhibitor therapy for treatment of advanced lung adenocarcinoma.8 Several genome-wide studies have implicated the role of protein kinase intracellular signalling pathways in the aetiology of bipolar disorder, and this association could potentially be a downstream effect of tyrosine kinase inhibitors.9

Conclusion

Little is known about neuropsychiatric adverse side effects from pazopanib or even tyrosine kinase inhibitor therapies. This case report serves to suggest the need to consider neuropsychiatric symptoms in patients receiving pazopanib therapy or other tyrosine kinase inhibitor treatment protocols and also to explore the underlying mechanisms.

We suggest that mania, which developed shortly after pazopanib administration, should be considered as a possible adverse drug reaction after excluding alternative causes of manic symptoms. Pazopanib should be stopped and the clinical situation reassessed, which was what was done in this case.

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Authors’ contributions

BLWT wrote the manuscript, AG conducted the patient interviews. All authors reviewed the final manuscript.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

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