Complex Case report Involving Polycythemia Vera, Myelofibrosis, Chronic Myeloid Leukemia, and Merkel Cell Carcinoma

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- **The landscape of hematologic oncology has been revolutionized by targeted therapies and immune checkpoint inhibitors (ICIs). However, their use in patients with complex, overlapping malignancies can unveil unprecedented challenges. Myeloproliferative neoplasms (MPNs) like polycythemia vera (PV) are driven by mutations in genes such as JAK2 and are associated with an increased risk of secondary cancers, both hematologic and solid [1]. The management becomes exceedingly complex when a patient develops a second, genetically distinct MPN like chronic myeloid leukemia (CML) while concurrently being treated for an aggressive solid tumor like Merkel cell carcinoma (MCC) with immunotherapy. We present a case that epitomizes this multi-layered complexity, highlighting the diagnostic dilemmas, therapeutic trade-offs, and unpredictable interactions between diseases and treatments**

• Case presentation

A 66-year-old woman was initially diagnosed with JAK2 V617F-positive polycythemia vera (PV). Her bone marrow biopsy at diagnosis already showed atypical hypercellularity and fibrosis, suggesting a propensity for progression. First-line treatment with hydroxyurea was initiated per standard guidelines [1]. However, within a year, her disease course was marked by poor control of her hematocrit, symptomatic thrombocytopenia, persistent aquagenic pruritus, and splenomegaly, defining hydroxyurea failure.
In February 2017, due to this inadequate response, therapy was switched to the JAK1/2 inhibitor ruxolitinib. Her symptoms, particularly pruritus and splenomegaly, improved initially. Two years into ruxolitinib treatment (September 2019), the patient was diagnosed with metastatic Merkel cell carcinoma. Immunotherapy with avelumab, an anti-PD-L1 monoclonal antibody, was commenced, which has shown high efficacy in this setting [4].
Remarkably, at the time of MCC diagnosis and avelumab initiation, routine blood work revealed dramatic new hematologic abnormalities: significant monocytosis, basophilia, and 5% circulating blasts. A urgent bone marrow biopsy was performed, revealing 4% blasts and hypercellularity with trilineage hyperplasia.

- **Cytogenetic studies confirmed a major new clonal event: the presence of the Philadelphia chromosome t(9;22) and a very high BCR-ABL1 transcript level (120% on the International Scale). Fluorescent in-situ hybridization (FISH) and PCR confirmed that the original JAK2 V617F mutation was still detectable, indicating the emergence of a separate CML clone rather than a single biphenotypic event, a rare but documented phenomenon [3].**
- **Given this definitive evolution to chronic phase CML, ruxolitinib was discontinued. Due to relatively stable blood counts, a decision was made to cautiously delay tyrosine kinase inhibitor (TKI) therapy. However, with the subsequent onset of worsening hyperleukocytosis, treatment with imatinib was initiated while avelumab for MCC was continued concurrently.**

In September 2020, the now 74-year-old patient was hospitalized with a splenic infarct, a known complication of both MPNs and CML, and persistent constitutional symptoms. A PET-CT scan to investigate inguinal lymphadenopathy showed no evidence of lymphoma or metastatic MCC. Her condition eventually stabilized with supportive care and anticoagulation. She was maintained on a regimen of imatinib, avelumab, and therapeutic anticoagulation. Despite over a year of imatinib therapy, molecular monitoring showed a limited response (e.g., failure to achieve a major molecular response), prompting consideration of switching to a second-generation TKI like dasatinib. However, the development of a new bilateral pleural effusion, a known adverse event of both dasatinib and less commonly, ICIs [5, 6], led to the deferral of this switch. The effusion was managed in collaboration with cardiology and resolved with diuretics and supportive care, attributed to a combination of factors.

Discussion

This case presents a triad of oncologic challenges: the progression of a JAK2+ MPN, the emergence of a BCR-ABL+ leukemia, and the diagnosis of a PD-L1+ neuroendocrine carcinoma. Its management navigates the intersecting toxicities and mechanisms of a JAK inhibitor, a TKI, and an ICI.
-First, the sequence of clonal evolution is intriguing. The emergence of the BCR-ABL1 clone became apparent precisely as immunotherapy was started. While this is likely coincidental, it raises the question of whether immune activation by avelumab could have influenced the bone marrow microenvironment, potentially un-masking a previously silent minor clone. There is growing evidence that TKI and targeted therapy can lead to off-target clonal selection [2], and the impact of ICIs on the hematopoietic niche is an area of active investigation.
-Second, the management of concurrent CML and MCC required careful balancing. Discontinuing effective immunotherapy for MCC was not an option given its metastatic nature. Therefore, running imatinib concurrently with avelumab was necessary. This combination was tolerated without overt synergistic toxicity in this case, but such data is scarce in the literature. The suboptimal response to imatinib could be multifactorial, potentially related to drug interactions, the underlying pro-inflammatory MPN background, or yet undefined mechanisms.
-Third, the adverse events—splenic infarction and pleural effusion—epitomize the diagnostic difficulty in such complex patients. The infarct could be attributed to the underlying MPN/CML-related hypercoagulable state, while the effusion could be a toxicity of a potential future drug (dasatinib), a rare toxicity of imatinib or avelumab, or related to cardiac dysfunction in an elderly patient.

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