EJCRIM
European Journal
of Case Reports
in Internal Medicine

METACHRONOUS OCCURRENCE OF ACUTE MYELOID LEUKAEMIA IN A CASE OF NEUROENDOCRINE TUMOUR

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Received: 07/02/2025
Accepted: 11/02/2025
Published: 10/03/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Consent has been obtained prior to treatment.
Acknowledgements: We sincerely acknowledge the contributions of the multidisciplinary team involved in the diagnosis and management of this case. Additionally, we express our gratitude to the patient and her family for their trust and cooperation throughout the treatment journey.
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How to cite this article: Menon A, Harindran Vallathol D, Charles D, Nair S, Kundil Veetil K, Komaranchath AS, Warrier AR. Metachronous occurrence of acute myeloid leukaemia in a case of neuroendocrine tumour. *EJCRIM* 2025;**12**:doi:10.12890/2025_005233

ABSTRACT

Haematological neoplasms are rare in patients undergoing peptide receptor radionuclide therapy (PRRT) for neuroendocrine neoplasms, though the long-term effects on bone marrow function remain an area of interest. We report the case of an elderly woman diagnosed with a pancreatic neuroendocrine tumour (pNET) who developed acute myeloid leukaemia (AML) while receiving PRRT. She was treated with a non-chemotherapy regimen of azacitidine and venetoclax, resulting in remission of both AML and the neuroendocrine tumour. This case highlights the potential risk of secondary haematological malignancies following PRRT and underscores the efficacy of a non-intensive therapeutic approach in managing AML in this context.

KEYWORDS

Neuroendocrine neoplasm, peptide receptor radionuclide therapy, acute myeloid leukaemia, dual malignancy

LEARNING POINTS

- This case highlights the sequential use of peptide receptor radionuclide therapy (PRRT) with octreotide in managing a metastatic neuroendocrine tumour (NET) and its transition to a chemotherapy-free regimen for secondary acute myeloid leukaemia (AML). The integration of targeted radionuclide therapy with molecular oncology approaches is an evolving treatment paradigm that can modify future medical practice.
- The case underscores the challenge of detecting therapy-related myeloid neoplasms in patients undergoing PRRT. The delayed diagnosis of AML due to pancytopenia highlights the need for vigilant haematologic monitoring in patients receiving long-term PRRT and somatostatin analogue therapy.
- The successful management of both malignancies showcases the importance of multidisciplinary tumour boards in decision-making. It emphasises the role of internists in coordinating oncology care, recognising complications and implementing individualised treatment strategies to improve patient outcomes.

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European Federation of Internal Medicine

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INTRODUCTION

Haematological neoplasms are rare in patients undergoing peptide receptor radionuclide therapy (PRRT) for neuroendocrine neoplasms, though the long-term effects on bone marrow function remain an area of interest. We report the case of an elderly woman diagnosed with a pancreatic neuroendocrine tumour (pNET) who developed acute myeloid leukaemia (AML) while receiving PRRT.

CASE DESCRIPTION

A 73-year-old woman with systemic hypertension, type 2 diabetes mellitus and hypothyroidism presented in February 2019 with dysgeusia and significant weight loss (8 kg over one year). Initial evaluation with abdominal ultrasonography revealed a hyperechoic lesion in the mid-pole of the left kidney, prompting further investigation. Contrast-enhanced computed tomography showed an 8.3 × 6 × 8.3 cm irregular, heterodense renal mass with local infiltration into the stomach, pancreas and spleen, suggestive of malignancy.

The patient underwent radical nephrectomy with distal pancreatectomy, splenectomy and gastric sleeve resection. Histopathology and immunohistochemistry confirmed a grade 2 well-differentiated neuroendocrine tumour (NET) involving multiple organs. A Ga-68 DOTANOC PET-CT scan identified a large para-aortic lymph node, gastric lymph nodes and a liver lesion, indicating metastatic disease *(Fig. 1)*.

First-line therapy with somatostatin analogues (2019–2020): The patient was started on monthly octreotide long-acting release (LAR) 30 mg injections. After six doses, reassessment by Ga-68 DOTANOC PET-CT showed an increase in para-aortic lymph node size, though liver lesions remained stable. She continued octreotide, but after 13 doses, repeat imaging showed new retrocrural lymph nodes, nodular surgical bed lesions and a cranial segment VII liver lesion, confirming disease progression.

PRRT (2020–2021): After a multidisciplinary tumour board (MDT) review, the treatment strategy shifted to 177-lutetium PRRT with continued octreotide. Following two cycles of PRRT, a Ga-68 DOTANOC PET-CT scan showed good response, leading to an additional two PRRT cycles. After four PRRT cycles and 23 doses of octreotide, reassessment imaging confirmed a stable disease, and the patient continued octreotide therapy *(Fig. 2)*.

Detection of AML (February 2022–onwards): During follow-up, the patient developed pancytopenia prompting a peripheral blood smear, which showed anisopoikilocytosis, dysplastic neutrophils and thrombocytopenia. A bone marrow biopsy revealed hypercellular marrow with increased myeloblasts (CD117 and MPO-positive), reduced erythroids and megakaryocytes, confirming AML *(Fig. 3)*. Cytogenetic analysis detected inversion 16 and trisomy 21, classifying it as a favourable-risk AML.

Non-chemotherapy AML treatment and ongoing monitoring (2022–present): The MDT recommended a chemotherapy-free regimen of azacitidine and venetoclax, considering the patient's age and comorbidity. After two cycles, bone marrow analysis revealed hypo-cellular marrow, minimal residual disease of 0.05% and no clonal abnormalities, suggesting remission. A concurrent Ga-68 DOTANOC PET-CT scan showed stable NET disease.

DISCUSSION

Therapy-related myeloid neoplasms secondary to PRRT are a multifactorial process. They originate due to errors in DNA repair mechanisms, loss-of-function genetic mutations or oncogene activation. The critical parameter is the differential sensitivities of deoxyribonucleic acid to radiation during the cell cycle and the variabilities in intrinsic host repair mechanisms[1]. As per studies, radioactivity in

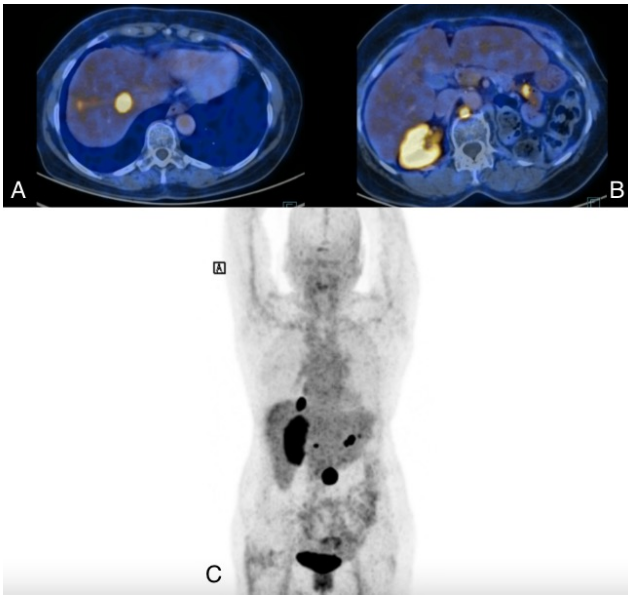


Figure 1. 68 Gallium DOTANOC scan showing: A) Avid homogeneously enhancing lesion in cranial aspect of segment VII of liver; B) Avid tiny nodular lesions noted along the surgical bed adjacent to remnant pancreatic tail and left renal fossa; C) Large para-aortic lymph node at the L3 vertebra level.

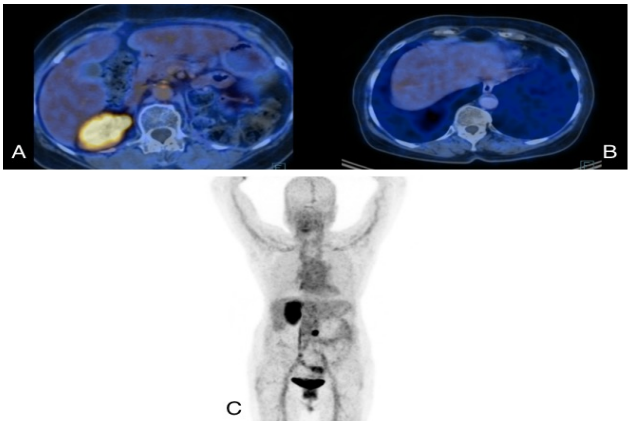


Figure 2. Ga-68 DOTANOC scan status post total 23 doses of octreotide injection and four sittings of 177Lu peptide receptor radiotherapy showing A) non-avid subcentimetric residual soft tissue adjacent to the remnant pancreatic tail and left renal fossa; B) Near complete resolution of previously avid lesion in the cranial aspect of segment VII of liver; C) Mild reduction in size and Gallium DOTANOC uptake of the para-aortic lymph node at the L3 vertebral level.

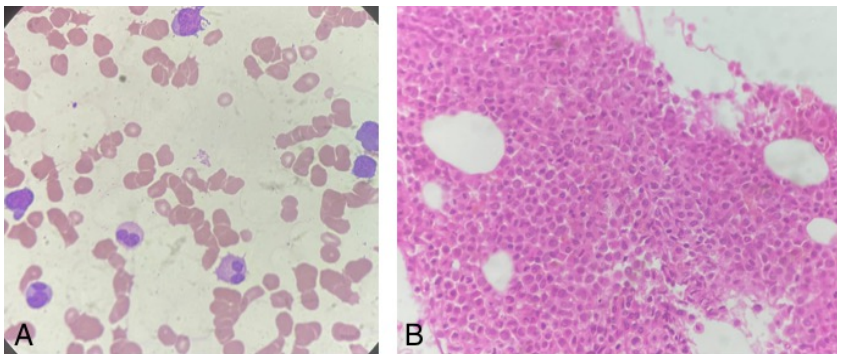


Figure 3. A) Bone marrow aspirate showing scattered eosinophils and blasts (Leishman stain, ×100 magnification); B) Bone marrow trephine biopsy showing diffuse immature cell infiltrate with increase in eosinophil precursors (H&E, ×20).

the blood is typically less than 1% and less than 20% in the blood and whole body, respectively, one day after PRRT. Thus, the cumulative red marrow and total body doses culminate at approximately 1 Gy and 1.5 Gy, respectively[2]. A clear dose–effect relationship has not been deciphered with radionuclide therapies such as PRRT. The dose used in treatment is clearly below the marrow threshold level, as noted in several studies. Hence, the dosimetry studies with PRRT have failed to predict myeloproliferative events post-PRRT. A key issue is the difficulty in accurately modelling bone marrow due to multiple confounding factors, such as pre-treatment with alkylating agents[1]. This issue might be partly resolved with PRRT being introduced in earlier lines of treatment for NETs.

Several studies have evaluated myeloid neoplasms after PRRT. One study assessing the long-term effects in 274 patients with gastroenteropancreatic neuroendocrine tumours GEP-NET reported that 4% of patients developed a haematologic neoplasm or otherwise unexplained persistent cytopenias, with a median latency of 41 months. A haematologic neoplasm (myelodysplastic syndrome, AML, myeloproliferative neoplasm) was seen in 2.9%, with a relative risk of 2.7[3]. In another meta-analysis of twenty-eight articles comprising 7,334 patients, the mean incidence of therapy-related myeloid neoplasms was 2.61%, and the median time of developing therapy-related myeloid neoplasm after the first PRRT treatment was mostly after one year[4].

Therapy-related acute myeloid leukaemia (t-AML) accounts for approximately 7% of patients with acute myeloid leukaemia. The most common cytogenetic abnormalities seen in t-AML include chromosome 5 and 7 abnormalities, mixed lineage leukaemia translocations and other complex cytogenetics. Those occurring after PRRT showed complex cytogenetics. Inversion 16 is a favourable-risk cytogenetic abnormality seen in approximately 5–10% of de novo AML patients; however, inversion 16 is extremely rare in t-AML[5].

CONCLUSION

Our patient – an elderly woman on octreotide and PRRT for a neuroendocrine tumour – developed AML. A latency period of around 15 months was noted from the first PRRT dose. Another important point we highlight is her exceptional response to the non-chemotherapy regimen of azacitidine with venetoclax, which she tolerated well. This is significant, as she had two critical negative risk factors for AML: advanced age and probable therapy-related leukaemia. She had inversion 16 and trisomy 21 in cytogenetics, both of which individually tend to portend a favourable prognosis but, in unison, may pose an adverse risk. These abnormalities separately usually do not occur in therapy-related leukaemias. While de novo AML remains a possibility, post-PRRT-induced AML cannot be completely ruled out. Moreover, we highlight the rarity of both diseases remaining in remission in this case.

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