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Challenges in the Management of Poorly Differentiated Neuroendocrine Tumors: A Comprehensive Clinical Approach

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Abstract

This manuscript addresses poorly differentiated Neuroendocrine Tumors (NETs), focusing on their complexity, clinical presentation, and diagnostic and therapeutic challenges. Despite their rarity, poorly differentiated NETs, including extrapulmonary small cell carcinomas, are notably aggressive, characterized by high mitotic rates and extensive necrosis. Commonly diagnosed in advanced stages, these tumors have a variable prognosis and are prone to early metastasis.

The first clinical case examines a 39-year-old patient whose advanced and metastatic disease underscores the importance of personalized treatment and the need for ongoing research. The second case, focusing on a neuroendocrine carcinoma, illustrates the tumor's aggressiveness and tendency to metastasize, even after an initially positive response to treatment. The choice of FOLFIRI as a second-line treatment reflects the need for an adaptive and multidisciplinary therapeutic approach.

The discussion highlights the diversity and complexity of NETs and the importance of early diagnosis. Treatment, tailored to the tumor's type, location, and grade, ranges from surgery and chemotherapy to radiotherapy, with an emphasis on platinum-based regimens and emerging immunotherapy.

In conclusion, the manuscript emphasizes the need for careful management and continuous research to improve medical outcomes and the quality of life of patients with these challenging tumors.

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Introduction

Neuroendocrine neoplasms, heterogeneous tumors originating from cells throughout the body, are rare but noted for their diversity and aggressiveness. The poorly differentiated Neuroendocrine Tumors (NETs) addressed in this study are characterized by high mitotic rates and extensive necrosis, often presenting in advanced stages. Their management is complicated by the lack of robust data, highlighting the need for further research to improve treatments and outcomes for these patients [1].

These tumors, including extrapulmonary small cell carcinomas, account for 2.5% to 5% of all NETs and are more commonly diagnosed in the seventh decade of life, with a slight male predominance. The five-year survival rate varies significantly, being up to 50% in localized cases but dropping considerably in advanced or metastatic stages, with a median survival of 5 to 38 months [2-4]. The Nordic NEC study [5] highlighted an overall survival of 11 months with chemotherapy. Factors such as functional status, cellular proliferation rate, and the primary location of the tumor influence survival. These tumors often metastasize early to the liver, bone, lung, and brain and are prone to post-treatment relapses, worsening the prognosis [2-4].

Poorly differentiated Neuroendocrine Tumors (NETs) arise from the neuroendocrine system and vary in their degree of differentiation. They frequently exhibit mutations in genes such as KRAS, TP53, and RB1 and are characterized by a high mitotic index and irregular nuclei. Approximately 30% of these NETs include non-neuroendocrine components. Despite the morphological differences between small and large cell subtypes, their prognosis is similar. These carcinomas, often metastatic and presenting with nonspecific symptoms, are found in various areas, including the pancreas, where they commonly show advanced disease at diagnosis [5,6].

They present with nonspecific symptoms and may include paraneoplastic syndromes such as Cushing's syndrome. Diagnosis employs imaging techniques like CT and PET scans, with PET ^{68}Ga-DOTATATE being particularly sensitive, and cerebral MRI is recommended due to the risk

of metastasis. Biopsy is crucial for confirmation and classification. Factors such as overall health status, hepatic metastases, and biochemical and genetic markers significantly influence the prognosis of these patients [7-10].

Treatments for poorly differentiated NETs, based on protocols for small cell lung cancer, include platinum-based chemotherapies and surgery in localized cases, followed by adjuvant chemotherapy with regimens such as cisplatin, etoposide, paclitaxel, and irinotecan, varying according to the disease stage [11-13].

For advanced but non-metastatic non-esophageal NETs, a multimodal treatment approach is recommended, including platinum-based chemotherapy, tailored radiotherapy, and surgery if feasible, with neoadjuvant radiotherapy due to the tumor's aggressiveness. In cases with metastasis, palliative chemotherapy with cisplatin or carboplatin and etoposide or irinotecan, typically for 4 to 6 cycles, is the preferred option [13]. The efficacy of cisplatin and carboplatin is similar, and in advanced treatments, combinations of immunotherapy such as ipilimumab and nivolumab are being explored. PD-1 or CTLA-4 inhibitors, used in immunotherapy, are particularly effective in patients with dMMR, MSI-H, or high TMB [14,15].

Temozolomide is often used as a second-line treatment, showing effectiveness in combination with other drugs. Given the limited options after platinum-based treatment and the potential of immunotherapy to achieve prolonged remissions, combinations such as nivolumab and ipilimumab or pembrolizumab are considered for advanced therapies [16]. Data interpretation must be cautious due to variations in studies, and the literature suggests the use of bevacizumab in advanced cases [17,18].

The treatment of poorly differentiated NETs requires a multimodal approach tailored to the stage and origin of the tumor. While treatments often follow protocols for small cell lung cancer, it's crucial to consider the specific characteristics of extrapulmonary tumors. Platinum-based chemotherapies are essential, but immunotherapy, particularly immune checkpoint inhibitors, is emerging as an important option in advanced treatments. Genetic tests like dMMR, MSI-H, and TMB are useful in identifying patients who may benefit more from immunotherapy, and ongoing research is key to improving treatment and prognosis for these patients [9].

Clinical Cases

First Patient

A 39-year-old male patient, an ex-smoker, presented with altered lower digestive transit featuring caprine-like stools for two weeks and intermittent hematuria. A CT scan revealed a solid peritoneal tumor in the pelvis (53 mm × 46 mm) infiltrating the bladder roof, retroperitoneal and pelvic lymphadenopathy, and multiple hepatic lesions suggestive of secondary involvement.

MRI showed a solid pelvic mass of 50 mm × 79 mm × 69 mm infiltrating the bladder roof, pre-vesical and iliac lymphadenopathy, hypovascular hepatic lesions indicative of metastases, and possible metastatic bone lesions in the pelvis.

Tumor Markers (MT): CEA: 315, CA 19-9: 1168.

Hepatic Biopsy (PBH) revealed poorly differentiated carcinoma with a proliferation index of 95%.

Immunohistochemistry (IHC): Focal CK20+, diffuse and intense for SATB2+, positive for neuroendocrine differentiation markers synaptophysin and chromogranin. Negative for GATA3 and CK7. Diagnostic conclusion: The immunophenotype supports the diagnosis of hepatic metastasis of poorly differentiated neuroendocrine carcinoma.

PET scan identified hypermetabolic hepatic lesions, predominantly in segment 2, and possible metastatic lymphadenopathy in the hepatic hilum and peripancreatic area. A hypermetabolic pelvic tumor was noted above the bladder, with bilateral iliac lymphadenopathy, the largest on the left side.

The patient commenced a specific oncological treatment based on carboplatin and etoposide.

Second patient

A 65-year-old female patient with a history of diet-controlled diabetes presented with right-sided pain, with no other notable symptoms, and was in excellent overall health. A CT scan revealed irregular thickening of the gallbladder wall with hepatic involvement and local infiltration. Secondary liver lesions of 7 mm to 15 mm and peripancreatic lymphadenopathy of 11 mm were noted, suggesting probable gallbladder carcinoma with hepatic metastases.

Tumor markers (MBT) showed normal levels of CEA, CA 19.9, and CA 125.

Liver biopsy identified high-grade carcinoma with neuroendocrine differentiation, high mitotic index, and immunohistochemistry positive for synaptophysin, negative for chromogranin A, INSM1 positive, and Ki-67 at 90%. The interpretation was small cell carcinoma of the gallbladder with neuroendocrine differentiation.

MRI revealed over 20 hepatic metastases and irregular thickening of the gallbladder wall. There was no biliary obstruction, lymphadenopathy, or ascites.

PET Ga-DOTATE scan showed multiple hepatic lesions, the largest in segment V, and thickening of the gallbladder without abnormal tracer uptake, indicating neuroendocrine carcinoma with Ki67 at 90%. No lesions expressed somatostatin receptors.

The patient was treated with cisplatin-etoposide, completing six cycles. PET-CT showed a complete metabolic response to the treatment.

Follow-up PET-CT identified neoproliferative activity with hypermetabolic thickening in the gallbladder and nodular lesions in hepatic segments, and CT of the brain revealed two focal lesions in the pons, warranting further evaluation with MRI.

MRI of the brain showed four intra-axial expansive lesions, two supratentorial and two infratentorial.

The patient underwent radiosurgery in four sessions and systemic chemotherapy with the FOLFIRI regimen, having received three cycles to date.

Discussion

In the first case, a 39-year-old patient with a poorly differentiated neuroendocrine tumor demonstrates the complexity and diagnostic challenges of these tumors, given their nonspecific clinical presentation, which includes digestive alterations and hematuria. Studies revealed advanced and metastatic disease, necessitating treatment with carboplatin and etoposide, in line with current

practices for high-grade tumors.

The second case, involving a patient with neuroendocrine carcinoma, highlights the aggressiveness and tendency toward metastasis of these tumors, underlining the importance of rigorous follow-up and an adaptive therapeutic approach, as evidenced by the choice of FOLFIRI as a second-line treatment. This case emphasizes the need for careful management and the adoption of a multidisciplinary approach, considering both the unpredictable nature of the tumor and the patient's quality of life.

Both cases illustrate the diversity and complexity of NETs, emphasizing that, although rare, they can occur at any age and require a high level of diagnostic suspicion. The long-term aggressiveness and early tendency to metastasize, coupled with the possibility of relapses after treatment, make the overall prognosis unfavorable. The importance of personalized treatment and ongoing research to improve medical outcomes and the quality of life of patients with these tumors is highlighted [6,19].

Conclusion

Poorly differentiated Neuroendocrine Tumors (NETs), although rare, are clinically significant with a variable presentation, including nonspecific symptoms and paraneoplastic syndromes. Their management requires accurate histopathological diagnosis and proper staging. Factors such as ECOG Performance Status, hepatic metastases, and biochemical markers influence treatment and prognosis. In resectable tumors, surgery and adjuvant systemic therapies are crucial, while in advanced stages, combinations of radiotherapy and chemotherapy are preferred. Chemotherapy regimens with cisplatin or carboplatin and etoposide are essential in metastatic cases. Despite advancements, more research is needed to develop more effective treatments and improve the prognosis and quality of life of these patients.

References

1. Rickman DS, Beltran H, Demichelis F, Rubin MA. Biology and evolution of poorly differentiated neuroendocrine tumors. Nat Med. 2017;23(6):1-10.
2. Eads JR. Poorly differentiated neuroendocrine tumors. Hematol Oncol Clin North Am. 2016;30(1):151-62.
3. Walenkamp AM, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. Cancer Treat Rev. 2009;35(3):228-36.
4. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063-72.
5. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013;24(1):152-60.
6. Dasari A, Mehta K, Byers LA, Sorbye H, Yao JC. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. Cancer. 2018;124(4):807-15.
7. Basturk O, Tang L, Hruban RH, Adsay V, Yang Z, Krasinskas AM, et al. Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. Am J Surg Pathol. 2014;38(4):437-47.
8. Smith J, Reidy-Lagunes D. The management of extrapulmonary poorly differentiated (high-grade) neuroendocrine carcinomas. Semin Oncol. 2013;40(1):100-8.
9. McNamara MG, Scoazec JY, Walter T. Extrapulmonary poorly differentiated NECs, including molecular and immune aspects. Endocr Relat Cancer. 2020;27(7):R219-38.
10. Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas. 2010;39(6):799-800.
11. Brennan SM, Gregory DL, Stillie A, Herschtal A, Mac Manus M, Ball DL. Should extrapulmonary small cell cancer be managed like small cell lung cancer? Cancer. 2010;116(4):888-95.
12. Volante M, Birocco N, Gatti G, Duregon E, Lorizzo K, Fazio N, et al. Extrapulmonary neuroendocrine small and large cell carcinomas: A review of controversial diagnostic and therapeutic issues. Hum Pathol. 2014;45(4):665-73.
13. Okumura T, Noguchi T, Sekiguchi N, Kobayashi T, Kanda S, Ida K, et al. Clinical analysis of extrapulmonary neuroendocrine carcinoma: A retrospective and single institution experience. Chemotherapy. 2023;68(2):87-94.
14. Fazio N, Abdel-Rahman O. Immunotherapy in neuroendocrine neoplasms: Where are we now? Curr Treat Options Oncol. 2021;22(3):19.
15. Gile JJ, Liu AJ, McGarrah PW, Eiring RA, Hobday TJ, Starr JS, et al. Efficacy of checkpoint inhibitors in neuroendocrine neoplasms: Mayo clinic experience. Pancreas. 2021;50(4):500-505.
16. Kobayashi N, Takeda Y, Okubo N, Suzuki A, Tokuhisa M, Hiroshima Y, et al. Phase II study of temozolomide monotherapy in patients with extrapulmonary neuroendocrine carcinoma. Cancer Sci. 2021;112(5):1936-42.
17. Lacombe C, Perrier M, Hentic O, Brixi H, De Rycke O, Cros J, et al. FOLFOX-bevacizumab chemotherapy in patients with metastatic neuroendocrine tumors. J Neuroendocrinol. 2023;35(1):e13227.
18. Raj N, Chan JA, Wang SJ, Aggarwal RR, Calabrese S, DeMore A, et al. Pembrolizumab alone and pembrolizumab plus chemotherapy in previously treated, extrapulmonary poorly differentiated neuroendocrine carcinomas. Br J Cancer. 2023;129(2):291-300.
19. Frizziero M, Kilgour E, Simpson KL, Rothwell DG, Moore DA, Frese KK, et al. Expanding therapeutic opportunities for extrapulmonary neuroendocrine carcinoma. Clin Cancer Res. 2022;28(10):1999-2019.