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Case Report

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A Complex Case of Neuroendocrine Carcinoma of the Cervix

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Abstract

This case report presents the clinical course of a 56-year-old woman admitted to the Emergency Department with a complex array of symptoms, including vaginal bleeding, muscular weakness, and severe back pain. Subsequent investigations led to the diagnosis of a highly malignant neoplasm, suspected to be microcellular carcinoma originating from the cervix/uterus. The patient exhibited metastases to the pulmonary parenchyma and cervical spine, necessitating a multidisciplinary approach for comprehensive management. The diagnostic journey involved imaging studies, including MRI and CT scans, and appropriate interventions, such as diagnostic curettage. Treatment modalities included radiotherapy and chemotherapy, resulting in notable clinical improvement.

Key words: Neuroendocrine carcinoma, Cervical cancer, Metastasis, Imaging, Radiotherapy, Chemotherapy

Introduction

Cervical carcinoma typically manifests as squamous cell carcinoma or adenocarcinoma. However, within the spectrum of cervical cancers, there exists a rare variant known as neuroendocrine cervical carcinoma (NECC). Cervical cancer encompasses several histologic types, of which the most common is squamous cell (70 percent)[1]. Adenocarcinoma and its variants account for about 25 percent of cases, while other histologic subtypes are uncommon. Cervical neuroendocrine (mainly small cell) tumors represent only about 2 percent of all cervical malignancies[2-6]. This distinctive subtype accounts for a small fraction of cervical malignancies, is a rare and aggressive malignancy, posing significant diagnostic and therapeutic challenges due to its propensity for early

metastasis. Small cell neuroendocrine carcinoma of the cervix is a rare disease, accounting for only up to 2 percent of all invasive cervical cancers[2-7]. In a series from the Surveillance, Epidemiology and End Results (SEER) database, the mean annual incidence in the United States from 1977 to 2003 was 0.06 per 100,000 women, compared with 6.6 and 1.2 for squamous cell carcinoma and adenocarcinoma, respectively[8]. Although the disease has been described in women from 22 to 87 years of age, the mean age at diagnosis of small cell neuroendocrine carcinoma of the cervix is about 45 years[9,10].

Clinical examination often reveals the presence of a pelvic mass, raising suspicions of local and distal disease spread. Additionally, some patients may present with paraneoplastic syndromes or involvement of distant organs such as the liver, adrenals, bone, bone marrow, or brain, further complicating the clinical picture. Patients with NECC present with vaginal bleeding, pelvic pain or feeling of pressure and with post sexual bleeding. NECC, characterized by its neuroendocrine differentiation, exhibits feature reminiscent of both epithelial and neuroendocrine cells. This type of cancer is characterized by a high frequency of lymph node metastases and early hematogenous dissemination. Human papillomavirus appears to be an etiology of these cancers. However, the exact mechanisms driving neuroendocrine differentiation and tumor progression remain incompletely understood, underscoring the need for further research and documentation of clinical experiences to enhance our knowledge base.

Despite advances in diagnostic modalities, the rarity of NECC poses challenges in its timely identification and management. Limited understanding of the disease's natural history and optimal treatment strategies further complicates clinical decision-making. Multidisciplinary collaboration involving gynecologic oncologists, radiologists, pathologists, and medical oncologists is paramount in formulating individualized treatment plans tailored to the patient's specific clinical presentation and disease burden. Treatment strategies for NECC encompass a combination of surgery, radiotherapy, and chemotherapy, depending on the extent of disease spread and overall patient condition. Surgical resection, including radical hysterectomy with pelvic lymphadenectomy, may be considered in localized disease settings. However, the aggressive nature of NECC often necessitates adjuvant therapies to target residual disease and mitigate the risk of recurrence.

In cases of metastatic NECC, radiotherapy and chemotherapy play pivotal roles in palliating symptoms and prolonging survival. Advanced radiotherapeutic techniques, such as volumetric modulated arc therapy (VMAT) and cone beam CT image-guided radiation therapy, offer precise targeting of tumor volumes while sparing surrounding healthy tissues, thereby minimizing treatment-related toxicities. Similarly, chemotherapy regimens incorporating platinum-based agents and etoposide have demonstrated efficacy in inducing tumor regression and improving patient outcomes. Small cell neuroendocrine carcinoma, first described in 1957, is the most common neuroendocrine tumor. The less common large cell variant, although histologically distinct, shares the same natural history and is treated similarly. The least common type of neuroendocrine cancer that arises in the cervix, a well-differentiated carcinoid tumor, exhibits the typical carcinoid features seen elsewhere in the body (non-existent or minimal cytologic atypia, rare or no mitotic figures, no necrosis), has a different natural history and treatment, and is discussed further in this case report. This case report details the intricate presentation, diagnostic process, and the subsequent management of a 56-year-old woman with metastatic neuroendocrine carcinoma involving the cervix, pulmonary parenchyma, and cervical spine. Small cell neuroendocrine carcinoma represents an extrapulmonary variant of small cell lung cancer.

Case Presentation

A 56-year-old woman presented to the Emergency Department with complaints of persistent vaginal bleeding over 12 days, accompanied by a month-long history of muscular weakness, difficulty in walking, and severe back pain. The patient's medical history included hypercholesterolemia, and her family history revealed her mother's demise from pancreatic cancer. Despite a normal Pap test a few months prior, the patient had sought medical attention multiple times in the preceding month for back pain and vaginal bleeding. Due to the persistence of symptoms, the patient underwent diagnostic curettage, revealing a highly malignant neoplasm with characteristics suggestive of microcellular carcinoma. Furthermore we conducted MRI of the lower abdomen which displayed an enlarged uterus with tumor-like formations, confirming cervical involvement. CT scans of the chest and upper abdomen revealed small formations in the pulmonary parenchyma, paravertebral masses, and a block of iliac lymph nodes, raising suspicions of secondary localizations and swollen pelvic nodes (23mm right, 17mm left) further indicated the extent of metastasis. Tumor markers were within normal ranges, except for a borderline elevation in Ca-125 (54.80 with a limit of 35 iu/ml). As for the treatment, following the comprehensive diagnostic process, the patient underwent five sessions of radiotherapy, employing VMAT and Cone Beam CT Image-Guided Radiation Therapy. Subsequently, three sessions of chemotherapy were administered. The treatment regimen resulted in a notable clinical improvement of symptoms.

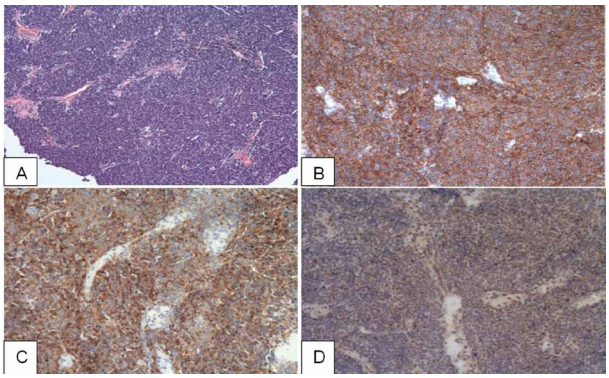

Figure 1. Histopathologic findings: A. hematoxylin & eosin stain B. CD 56 marker C. synaptophysin marker D. chromogranin marker.

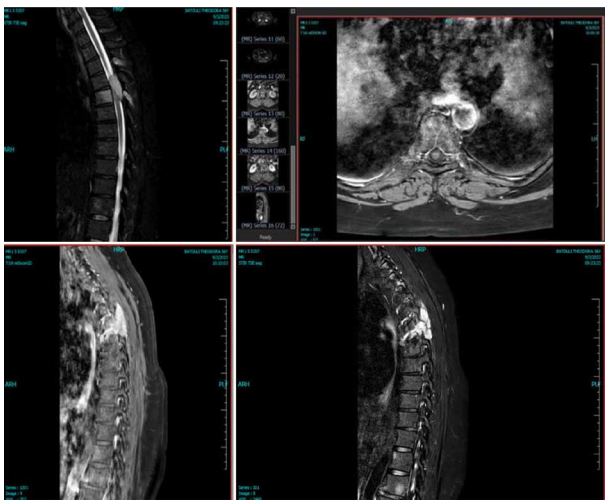

Figure 2. MRI of spinal cord with the bone metastasis in T1,T2 sequences.

Conclusion

In conclusion, the presented case report underscores the challenges and complexities involved in diagnosing and managing neuroendocrine carcinoma of the cervix, particularly in its metastatic form. This rare variant of cervical cancer, though comprising a small percentage of cases, presents unique diagnostic dilemmas and therapeutic considerations due to its aggressive nature and propensity for early dissemination.

The clinical presentation of the 56-year-old woman in this case exemplifies the heterogeneous manifestations of neuroendocrine cervical carcinoma, including vaginal bleeding, muscular weakness, and severe back

pain. Despite a normal Pap test, the persistence of symptoms prompted further investigation, leading to the eventual diagnosis through diagnostic curettage and imaging studies. These findings highlight the importance of maintaining a high index of suspicion for rare malignancies, especially in patients with atypical symptoms or risk factors.

The diagnostic journey outlined in this case report illustrates the pivotal role of imaging modalities such as MRI and CT scans in delineating the extent of disease involvement, including cervical, pulmonary, and paravertebral metastases. Additionally, the detection of elevated tumor markers, notably Ca-125, albeit borderline, underscores the utility of adjunctive laboratory investigations in the diagnostic workup of neuroendocrine cervical carcinoma. Multidisciplinary collaboration is paramount in formulating an effective treatment strategy for metastatic neuroendocrine cervical carcinoma. The integration of radiotherapy and chemotherapy, as evidenced in this case, represents a comprehensive approach aimed at targeting both local and systemic disease burden. The utilization of advanced radiotherapeutic techniques, including VMAT and Cone Beam CT Image-Guided Radiation Therapy, underscores the importance of precision medicine in optimizing treatment outcomes and minimizing treatment-related toxicity.

Comparing this case report with existing literature in the international bibliography reveals several commonalities and nuances. Consistent with prior studies, neuroendocrine cervical carcinoma predominantly affects women in their fifth decade of life, although cases have been reported across a wide age range. The rarity of this malignancy underscores the limited understanding of its pathogenesis and optimal management strategies, necessitating continued research and documentation of clinical experiences.

Moreover, the pattern of metastatic spread observed in this case aligns with existing literature documenting the propensity for lymphatic and hematogenous dissemination in neuroendocrine cervical carcinoma. Parallels can also be drawn with extrapulmonary small cell carcinoma, particularly in terms of treatment approaches and clinical outcomes. Nevertheless, it is essential to acknowledge the limitations of this case report, including its retrospective nature and the inherent biases associated with single-center experiences. Additionally, the relatively short-term follow-up period precludes definitive conclusions regarding long-term prognosis and treatment efficacy.

In summary, this case report contributes to the evolving understanding of small cell neuroendocrine carcinoma of the cervix by presenting a detailed account of its clinical manifestation, diagnostic challenges, and the efficacy of a multimodal therapeutic approach. The rarity of this malignancy underscores the importance of disseminating knowledge to enhance clinical suspicion, facilitate early diagnosis, and guide the implementation of targeted therapeutic interventions for improved patient outcomes.

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