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Case Report

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Beyond the Boundaries: A Case Report of Dedifferentiated Endometrial Carcinoma Masquerading as A Neurological Disorder

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Abstract

Background: *Dedifferentiated endometrial cancer (DEC) poses significant clinical challenges due to its atypical presentation and aggressive metastatic behaviour, often leading to diagnostic dilemmas, especially when presenting with unusual symptoms.*

Case Presentation: *A female in her 50s with a history of hypertension and obesity exhibited clinical symptoms that suggested seizures. However, further diagnostic imaging revealed lesions in the abdomen, chest, and pelvic region, as well as evidence of multiple brain invasions and pulmonary nodules. Biopsy results confirmed the presence of an extensive malignant disorder characterized by poor differentiation and aggressive activity.*

The neurological symptoms observed in the patient resembled those of a seizure disorder but lacked typical characteristics. This unusual presentation and rapid disease progression highlighted the clinical significance of the case, emphasizing the complexity of the condition and the need for thorough differential diagnosis in such scenarios.

Conclusion: *This case study highlights the aggressive nature of DEC and emphasizes the importance of a multidisciplinary approach and comprehensive evaluation in managing challenging cases of endometrial cancer. The study underscores the complexities associated with DEC and its misleading symptoms, providing valuable insights into medical literature. Ultimately, it advocates for enhanced clinical vigilance and tailored management strategies in similar cases.*

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Dedifferentiated Endometrial Cancer, Poor Differentiation, Seizures, Brain Invasion, Pulmonary Nodules.

Introduction

Dedifferentiated endometrial carcinoma (DEC) is a rare and aggressive type of endometrial cancer [1] characterized by the presence of undifferentiated and transformed parts within the malignancy [2]. Typically, post-menopausal women experience symptoms such as irregular uterine bleeding and pelvic pain [3]. Due to its aggressive nature and tendency to spread quickly, DEC usually has a poor prognosis [4]. While metastases to organs like the brain, lungs, and liver are possible but rare, their occurrence significantly impacts the disease prognosis. The metastatic nature of DEC poses challenges in treating the condition [4].

This case report aims to highlight a highly unusual example of dedifferentiated endometrial cancer with extensive metastases affecting vital organs. The patient's chief complaint was seizure-like reactions without typical seizure symptoms. This unique case provides valuable insights into the diverse presentations of DEC and underscores the need for a comprehensive approach to identifying and developing a treatment plan.

Case Presentation

A woman in her 50s with a medical history of obesity and hypertension was the subject of the case study. The patient was transferred to our institution from another hospital by Emergency Medical Services for a neurosurgical evaluation due to brain metastases being discovered.

The patient's initial complaint at the previous facility was altered mental status, which led to a CT scan of the brain and subsequently, transfer to our facility for neurosurgical evaluation.

Upon arriving at our facility, the patient was disoriented and unable to recall her name or birthdate. She reported feeling "shaking" and described experiencing an "out of body experience" during the shaking spell. She denied any previous similar episodes, seizures, or strokes. The patient also reported no recent falls, loss of consciousness, tongue biting, or incontinence, which are typical seizure symptoms.

The patient's mental state improved the morning after being admitted to the hospital. Before this event, the patient had no significant medical history apart from obesity and hypertension.

During the patient's hospital stay, she underwent a CT scan of the head, followed by an MRI of the brain/head, and a whole-body CT scan. The findings from these imaging studies prompted a CT-guided core biopsy of the right lung and of the vaginal tumor and endometrial curettage, all of which aided in making diagnoses.

Clinical Findings

Laboratory findings:

The laboratory findings are outlined in Table 1, including the blood counts and chemistry data at the presentation time. The initial lab work showed elevated tumor markers (CA 15-3, CA 19-9 and CA 125), raising suspicion of a malignant abnormality in this case.

Hematology	
WBC	10.03
RBC	3.91
Hgb	11 g/dL
Hct	34.6
MCV	88.5 fL
MCH	28 pg
MCHC	31.8 g/dL
Platelets	331
MPV	10.1 fL
RDW	14.9
Chemistry	
Anion Gap	14.2
Sodium	139 mmol/L
Potassium	3.4 mmol/L
Chloride	103 mmol/L
CO2	21.8 mmol/L
Calcium	9.7 mg/dL
BUN	17.5 mg/dL
Creatinine	1.1 mg/dL
BUN/Cr	15.91
Glucose	166 mg/dL
Protein	8 g/dL
Albumin	3.7 g/dL
Globulin	4.3 g/dL
ALT	9 U/L
AST	25 U/L
Alk Phos	85 U/L
Bilirubin	0.5 mg/dL
eGFR	59 mL/min/1.73m2
TSH	3.27 UIU/ML
Coagulation	
PTT	30.1 seconds
PT	10.9 seconds
INR	0.99 seconds
Infectious Disease	
COVID-19	Negative
Influenza PCR	Negative
RSV PCR	Negative
Tumor Markers	
AFP	<3.00 ng/mL
CA 125	79.9 unit/mL
CA 15-3	57.2 unit/mL
CA19-9	50.2 unit/mL
CEA	<2.0 ng/mL
Lipids and CV risk	
Cholesterol	218 mg/dL
HDL cholesterol	38.4 mg/dL
Chol/HDL	5.34 mg/dL

LDL Calculated	149.6 mg/dL
Triglycerides	90.6 mg/dL
VLDL calculation	18.12 mg/dL

Imaging and Diagnostic Findings

A series of imaging studies were crucial in understanding the patient's condition:

CT head: Figure 1

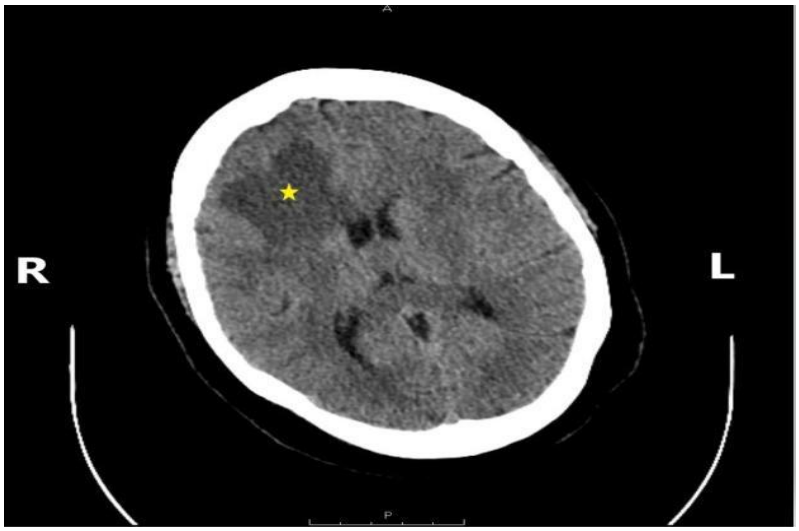

Figure 1: CT Head with lesion and mass effect (star).

The computed tomography (CT) scan of the head showed several masses inside the skull. The largest one, measuring up to 2 cm, was found in the right frontal lobe. Additionally, smaller lesions were seen in both parietal lobes.

There was also some swelling around the masses, but no evidence of bleeding. These findings strongly suggest the presence of cancer that has spread to the brain. Further tests with MRI are recommended for more detailed information.

MRI Brain (with and without Contrast): Figure 2

The scan revealed multiple intra-axial enhancing masses. The largest lesion, measuring 2.3 cm, was located in the right frontal region, with other masses found in the right parietal region and the left cerebellum. The largest mass in the right frontal region was surrounded by significant edema, and there was also a mild mass effect and a subtle focal midline shift to the left.

It's important to note that no findings suggestive of an acute infarct were noted on the diffusion-weighted sequence, which is critical information for the differential diagnosis.

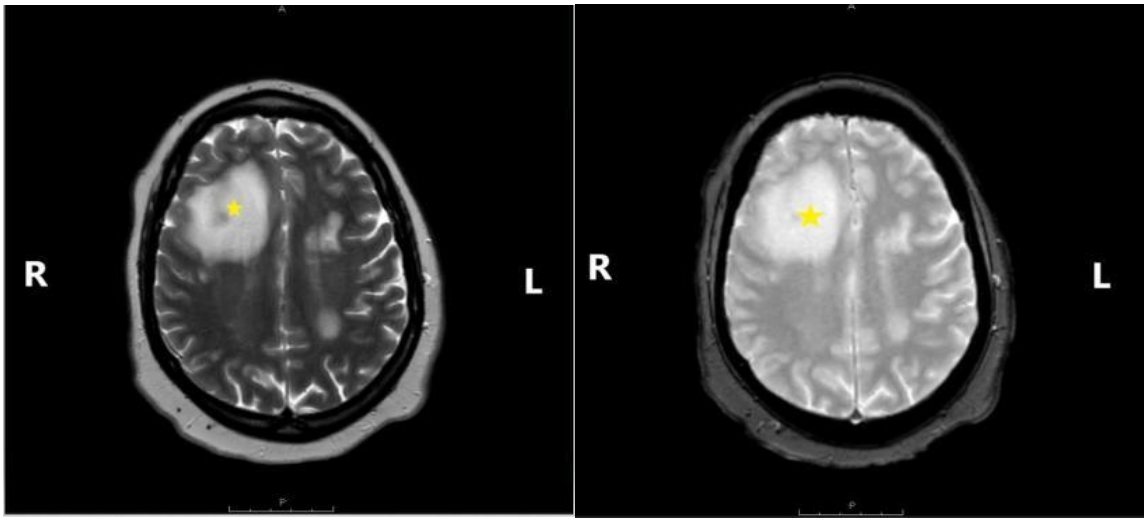

Figure 2: MRI Head with lesion in right frontal lobe (Star).

CT Chest/Abdomen/Pelvis: Figure 3 and Figure 4

The scan showed that there were multiple small nodules in the lungs. The largest nodule, measuring 1.7 cm, is located in the lower lobe of the right lung and is highly suggestive of being a sign of cancer spreading to the lungs.

There are also signs of enlarged lymph nodes in the central part of the chest, indicating potential cancer involvement. In addition, there is a small amount of fluid in the right lung and a thickening of the tissue covering the right side of the chest.

The scan also revealed abnormal thickening of the endometrium (4.4 cm), which is a cause for concern in a postmenopausal patient. Additionally, there is a cystic mass in the left side of the pelvis and enlarged lymph nodes near the left pelvic bone. Lastly, a small abnormality was found in the left lobe of the liver, but it was too small to be definitively identified using this imaging technique.

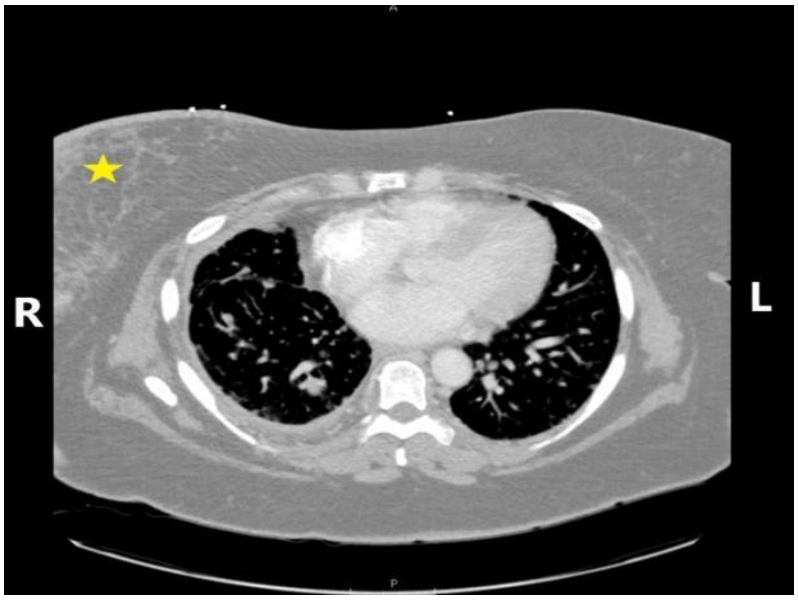

Figure 3: CT chest with lung nodule and thickened right breast (Star).

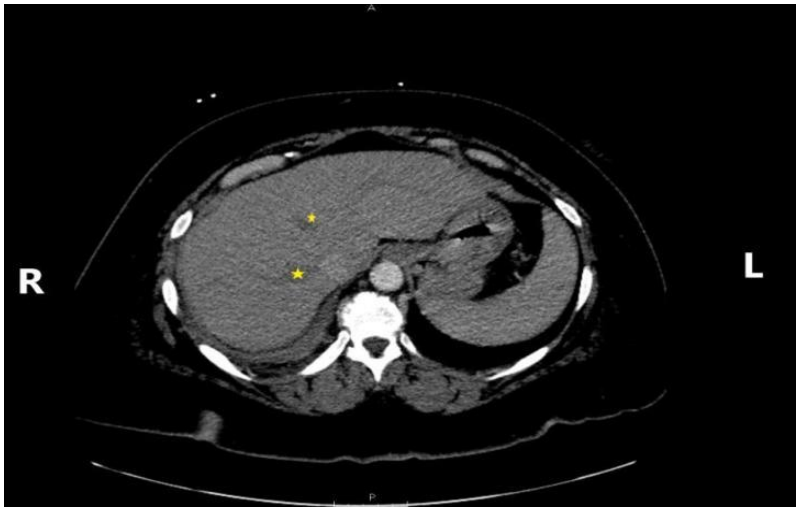

Figure 4: CT abdomen with hypo-attenuating liver lesions (Stars).

Right lung mass, CT guided core biopsy: Figure 5

Poorly differentiated carcinoma, consistent with metastatic carcinoma from dedifferentiated endometrial carcinoma.

Comments: The biopsy shows generous fragments of alveolated lung tissue and both viable and non-viable tumor cells. The neoplastic cells have an epithelioid morphology with enlarged, hyperchromatic nuclei and moderate eosinophilic cytoplasm, and they grow in sheets and perivascular spaces. Atypical mitotic figures are present.

There is no evidence of glandular differentiation. Immunohistochemical analysis confirms that the tumor cells are epithelial, showing positivity for cytokeratin OSCAR with focal expression of CK7, and negativity for CK20, TTF-1, ER, GATA-3, P40, PAX8, CD56, synaptophysin, HMB-45, MART-1 and SOX-10. P53 shows a wild type staining pattern.

In summary, the tumor's morphology and immunophenotypic features resemble the undifferentiated component of endometrial differentiated carcinoma and are most consistent with metastases from the carcinoma.

Vaginal tumor biopsy and D&C Pathology report: Figure 6, Figure 7, Figure 8.

a. **Vaginal tumor Biopsy:** Involvement by undifferentiated carcinoma from endometrial dedifferentiated carcinoma.

Comments: Histologic sections show fragments of high-grade undifferentiated carcinoma with extensive necrosis. The tumor is partially covered by squamous mucosa, indicating invasion of the vagina (metastasis), rather than a fragment dropped off from the uterine cavity. The morphology is similar to the undifferentiated component in the endometrial curetting specimen (see part B below).

b. **Endometrial Curettings:** Endometrial dedifferentiated carcinoma.

Comments: Histologic sections show a biphasic tumor with two distinct components. The first component is a differentiated endometrioid adenocarcinoma with an overall FIGO grade 2, containing areas of lower grade (FIGO 1). The differentiated component displays recognizable glandular architecture, moderate amounts of basophilic cytoplasm, and round to oval nuclei with occasional prominent nucleoli. Immunohistochemistry confirms this as as endometrioid carcinoma by demonstrating strong, diffuse positivity for ER, PR, and PAX8. The undifferentiated component consists of high-grade epithelium arranged in nests and trabeculae, accompanied by a marked stromal desmoplastic reaction and geographic necrosis. These cells show round to oval morphology with increased nuclear-to-cytoplasmic ratio, hyperchromatic nuclei, and readily identifiable atypical mitotic

figures. Immunohistochemistry reveals diffuse expression for pancytokeratin OSCAR with limited CK7 expression and negativity for synaptophysin, CD56, chromogranin, ER, PR, and PAX8. Patchy reactivity for p16 is noted, while p53 shows a wild-type pattern.

MMR immuno-stain reveals intact nuclear expression of MLH1, MSH2, and MSH6 in both components and intact nuclear expression of PMS2 as well, suggesting a clonal relationship between the differentiated and undifferentiated components.

In conclusion, the histologic and immunohistochemical findings are consistent with endometrial dedifferentiated carcinoma. Clinical and imaging findings should be considered for further correlation.

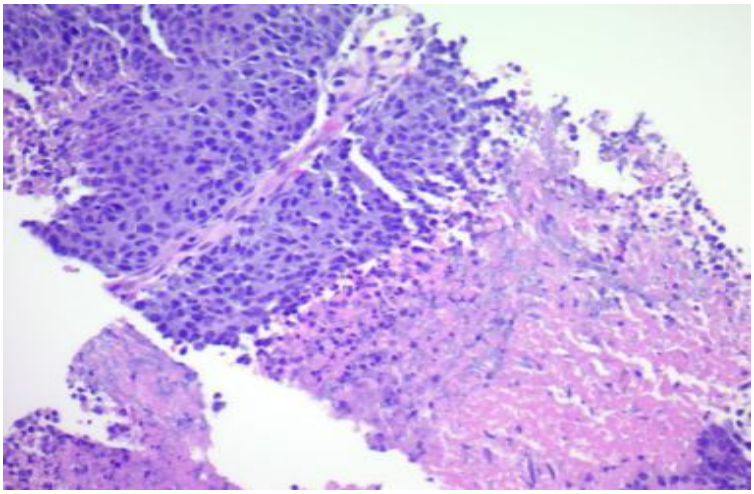

Figure 5: Right lung mass, CT guided core biopsy depicting Poorly differentiated carcinoma.

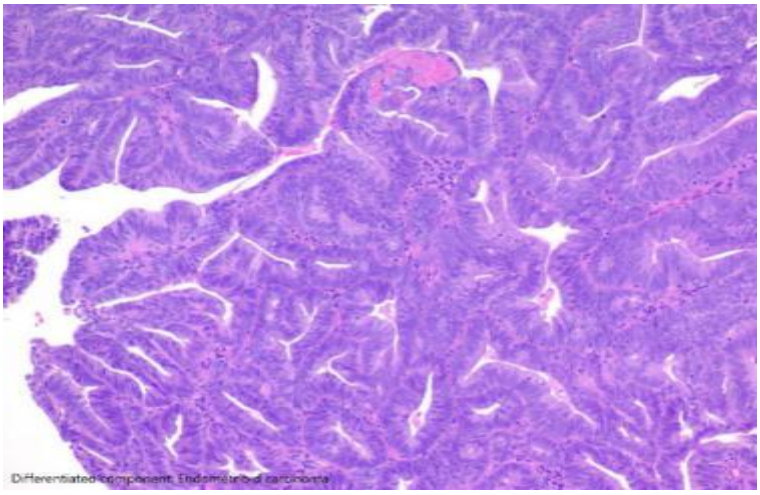

Figure 6: Dedifferentiated component Endometrial carcinoma.

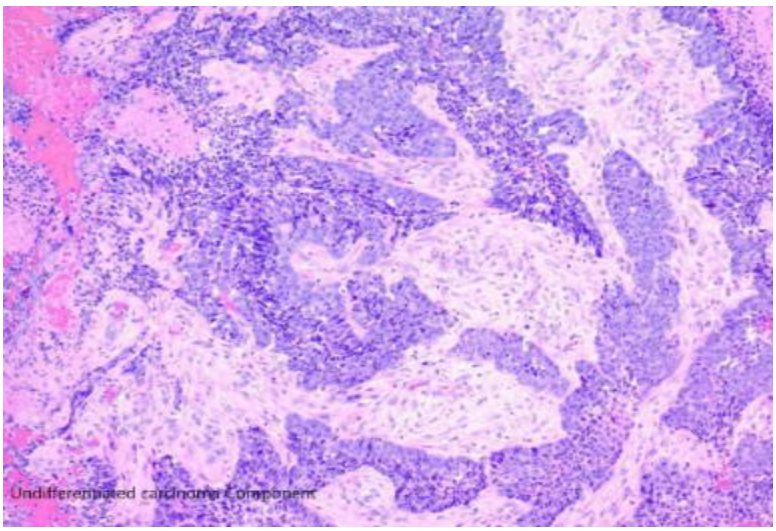

Figure 7: Undifferentiated Carcinoma component.

AJCC 8th Edition: Stage IV cT3b cN1a cM1, FIGO Stage IIIC1, Grade 3, pMMR, ER- PR-.
CARIS Testing: pMMR and MSI stable. Other pathogenic variants seen: ARID1a Exon 9 p.I934fs, ARID1a Exon 20 p.K1953fs, CTNNB1 Exon 3 p.S33C, KRAS Exon 2 p.G12V, PIK3CA Exon 10 p.E545K, PTEN Exon 2 p.G36, PTEN Exon 3 p.H61R, TMB Low- 3%.

Discussion

DEC was initially described in 2006 and is estimated to account for 1-9% of all endometrial carcinomas [1]. Patients with DEC typically present at a later stage and experience early recurrences compared to conventional endometrioid carcinomas [1,15].

The aggressive clinical behavior and poor prognosis of DEC are determined by the undifferentiated component, even if it is present in a small proportion (as low as 20%) [3]. DEC is characterized by a combination of high-grade undifferentiated carcinoma and low-grade endometrioid carcinoma [5,16]. It's important to note that the lack of a clear definition of the histological features that set apart dedifferentiated endometrial carcinoma from other tumors, such as high-grade endometrioid adenocarcinoma, has contributed to poor recognition of this neoplasm, making it quite challenging to diagnose [14,17].

In the classic presentation of DEC, postmenopausal hemorrhage, pelvic discomfort, and symptoms associated with a pelvic mass are frequently observed. The metastatic type of DEC often affects the lungs, abdominal surfaces, and regional lymph nodes [6].

The development of DEC is not well understood, but it is believed to occur due to the dedifferentiation of an existing low-grade endometrioid carcinoma [1,10]. Molecular studies have indicated that DEC often involves mismatch repair deficiency, which suggests a potential benefit from immunotherapy [3,11,18]. However, the best treatment approach for DEC is not well-defined, and most cases involve a combination of surgery, chemotherapy, and radiation therapy [1,10].

DEC is histologically characterized by a distinct shift from the low-grade endometrioid component to the undifferentiated component, which shows no signs of differentiation [1].

The case presented in this report is considered exceptional and rare due to its clinical presentation and widespread malignant nature. Most documented cases of DEC-related malignancies are confined to local pelvic tissues and lymph nodes [7]. However, there have been reports of advanced-stage endometrial carcinoma involving the central nervous system [12,13,14]. Piura et al. studied 115 cases of DEC and found that in the vast majority of cases with central nervous system involvement, brain metastasis was observed after the diagnosis of endometrial carcinoma, with a median time interval of about 17 months [12]. The present case is different in that brain metastasis was the initial discovery, leading to further investigation and the subsequent identification of the endometrial tumor.

The unusual symptoms in this case set it apart from previously reported cases. The presentation of neurological signs resembling seizure-like activity but without the classic indications of seizures is rare for DEC [8]. Furthermore, the absence of disorientation after the episode and a quick return to a normal state of mind differentiate it from a traditional seizure [8]. Typically, neurological symptoms are uncommon in DEC cases unless the central nervous system is significantly involved. The rapid progression and aggressiveness of the disease are evidenced by the extensive presence of metastases at the time of confirmation in this case. While DEC is known to act aggressively, there are few reports of it spreading so extensively [9].

Additionally, the extensive lesions in the lungs, liver, brain, vagina, adnexa, and the pleura make this specific case exceptional.

Overall, the disorder is challenging to detect as endometrial cancer typically does not manifest neurologically and lacks the typical symptoms associated with the disease.

Follow-Up

After the in-patient evaluation, the neurosurgery team recommended against surgical intervention. The patient was prescribed Keppra (Levetiracetam) 750 mg twice a day and a taper of Decadron (Dexamethasone). The Decadron taper started with 4 mg three times a day for 48 hours and then reduced to 2 mg three times a day for maintenance. This treatment aimed to prevent seizures and manage brain swelling.

The gynecology oncology team suggested systemic therapy, palliative radiation, or palliative/hospice care before the patient's discharge from the hospital. Following this, the patient received stereotactic radiation therapy 30 Gray in 5 fractions as an outpatient with the radiation oncology team. The patient also received outpatient care from the medical oncology team, but she declined and continues to decline systemic therapy.

Conclusion

Dermatofibrosarcoma protuberans (DEC) can be identified by the presence of unusual seizure patterns and metastasis that involves the brain, liver, and lungs. This case illustrates the importance of considering all possible diagnoses in oncology patients, particularly those with atypical presenting symptoms. The rapid growth, unusual presentation, and widespread metastasis of this patient's DEC offer new insights into the literature. It also emphasizes the necessity for further research and awareness of this type of cancer.

Conflicts of Interests: The Authors declare that there are no competing interests.

Patient Consent: Written informed consent for publication was obtained from the patient

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Author contribution: Jerry Kenmoe and Zahid Hussain were responsible for drafting the manuscript, Mohamed Belal and Israel Umoh were responsible for editing the manuscript and collection of supplementary data (pathology slides and laboratory data). Jeffrey Borgeson was responsible for supervision and concept design of the manuscript.

Ethics: The research and manuscript were conducted as per the McLaren Regional Healthcare system ethics guidelines and was approved by the McLaren Regional Healthcare System Ethics committee.

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