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Merkel Cell Carcinoma With Isolated Pancreatic Metastasis

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Abstract

Merkel cell carcinoma (MCC) is a highly aggressive cutaneous neuroendocrine carcinoma, frequently associated with distant metastasis. However, recurrence of MCC manifesting with only pancreatic involvement is exceedingly rare. A 53-year-old man presented to our institution with abdominal discomfort 3 months after initial resection of chest wall MCC. Imaging revealed lesions in the pancreas and peripancreatic lymph nodes. Pathology obtained through endoscopic ultrasound confirmed recurrence of MCC. He underwent chemotherapy with cisplatin and etoposide, resulting in a complete resolution of the pancreatic lesions. Unfortunately, he passed away from sudden cardiac arrest while being in remission from MCC. Immunohistochemistry is crucial in differentiating MCC from primary pancreatic glandular and neuroendocrine tumors. While there are no definitive guidelines in the management of pancreatic lesions associated with MCC, checkpoint inhibitor immunotherapy is increasingly being used.

Keywords

Merkel, carcinoma, pancreas, metastasis, immunotherapy

Introduction

Merkel cell carcinoma (MCC) is a highly aggressive primary skin neuroendocrine cancer that is associated with a high risk of locoregional and distant spread, and an overall poor prognosis. Distal metastases are frequent in the natural history of MCC, and the most common sites involved are distant lymph nodes, liver, lung, bone, and brain. Although uncommon, there are reports of pancreatic lesions in patients with metastatic MCC, typically with multiple other foci of metastases. We report a rare case of relapse of MCC, manifesting with isolated pancreatic involvement and mimicking pancreatic cancer. We also summarize additional cases reported in the literature.

Case Description

A 53-year-old Caucasian gentleman presented with a 9-month history of an enlarging crusting lesion on the anterior chest wall. Physical examination showed a 15 × 20 cm crusty erythematous skin lesion in the upper mid-chest. He also had palpable right axillary and left pre-clavicular lymphadenopathy. He underwent wide local excision with bilateral axillary and left neck lymph node dissection. Surgical pathology revealed lymph node–positive stage, pN3 MCC (pTNM, American Joint Committee on Cancer, 8th edition) with a small focus of squamous cell carcinoma. All resected margins were negative. He was started on adjuvant radiation therapy (RT) after discussion in the multidisciplinary tumor board but presented after starting RT (3 months after initial diagnosis) with new upper abdominal discomfort.

On presentation, vital signs were within normal limits. Physical examination was without significant abdominal findings. Laboratory results revealed mildly elevated lipase of 89 U/L (reference 5-55 U/L). Other laboratory results, including liver function tests, were within normal limits. CA 19-9 level was 15 U/mL (reference 0-35 U/mL).

Computed tomography (CT) scan of the abdomen revealed areas of hypoattenuation in the pancreas with

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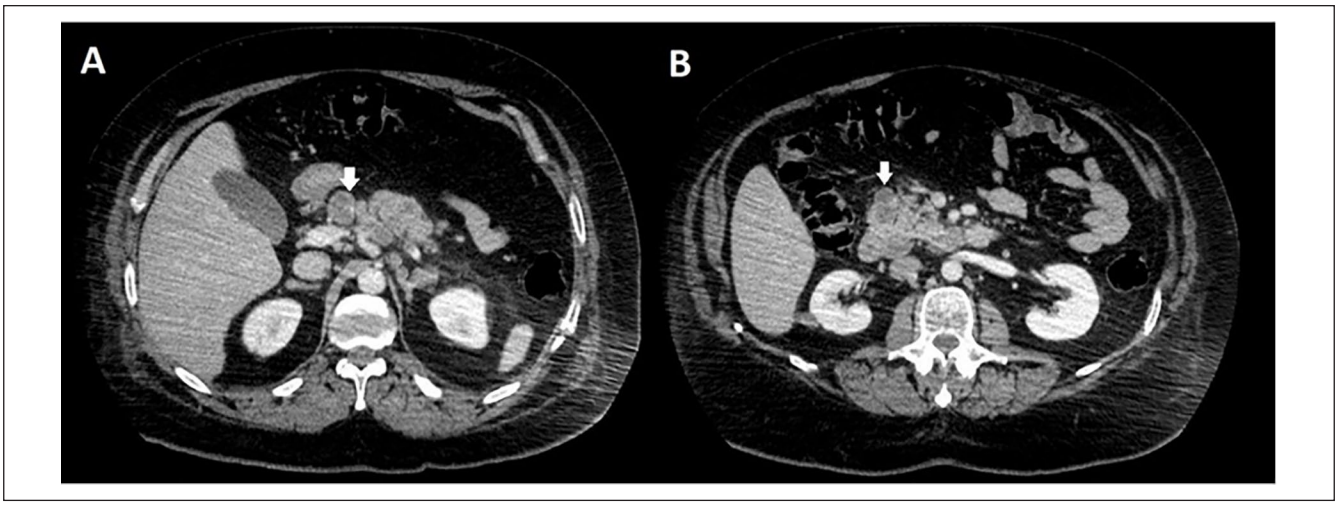

Figure 1. Computed Tomography of abdomen with contrast, initial. (A) Peripancreatic lymph node, measuring 2.6 cm × 2.0 cm. (B) Ill-defined area of low attenuation in the pancreatic uncinate process measuring 2.3 cm × 1.9 cm.

enlarged peripancreatic lymph nodes (Figure 1). Endoscopic ultrasound (EUS) showed similar findings. EUS-guided fine needle aspiration (FNA) showed malignant cells morphologically and immunohistochemically similar to his initial primary cancer, consistent with MCC (Figure 2).

He underwent 6 cycles of chemotherapy with cisplatin/etoposide with complete resolution of the pancreatic masses and lymphadenopathy (Figure 3). However, 1 month after his sixth cycle of chemotherapy, and 5 months after the diagnosis of pancreatic metastases, he passed away due to sudden cardiac arrest at home.

Discussion

Merkel cell carcinoma is a rare cutaneous neuroendocrine carcinoma that is believed to originate from epidermal neuroendocrine mechanoreceptors called Merkel cells.[1,2] It was first described in 1972 by Toker.[3] It has a high propensity for local recurrence, regional lymph node, and distant metastases.[4] The incidence of MCC has been increasing in recent years and is estimated to be around 0.18 to 0.41/100000.[5] Increased incidence of MCC during the past 2 decades may reflect improved diagnostic techniques, especially immunohistochemistry.[5]

Risk factors for MCC include older age,[1] male gender,[5] fair skin,[5] ultraviolet light,[6] immunosuppression (in particular, kidney transplant,[7] lymphoproliferative malignancy,[6] and AIDS[8]), and radiation exposure.[9] In a SEER (Surveillance, Epidemiology, and End Results) database study of 3870 cases, 94.9% of patients were Caucasian between 60 and 85 years of age.[5] High levels of Merkel cell polyomavirus DNA were found in tumor samples in about 80% of cases of MCC.[8] Clonal integration of the virus may lead to malignant transformation and has prognostic significance.[2,8,10]

There is an increased reciprocal risk of MCC with other primary cancers, mainly other skin cancers and certain hematologic malignancies.[11] This may represent shared risk factors such as ultraviolet light and immunosuppression.[12] Interestingly, in our patient, surgical pathology revealed a focus of moderately differentiated squamous cell carcinoma, adjacent to MCC.

MCC typically presents as a violaceous nodular or plaque-like lesion in the sun-exposed parts of the body.[1] Involvement of lymph nodes is the strongest prognostic factor for survival and risk of developing metastatic disease.[13] About 75% to 83% of MCC patients eventually develop regional nodal and distant metastasis.[4] Sites of metastases frequently involved include distant lymph nodes, liver, lung, bone, and brain.[13] A recent study that analyzed the pattern of distant metastasis in 215 patients with metastatic MCC found that 8% of the cases had pancreatic involvement.[14]

MCC accounts for a minuscule portion of pancreatic neoplasms. Adsay et al[15] reported 1 case of MCC among 973 surgical specimens of pancreas. Out of 4955 adult autopsy cases in the same study, there were 190 cases of pancreatic tumors, none with MCC. Raymond et al[16] reported a single case of MCC among 221 patients who were diagnosed with a pancreatic malignancy via FNA/core needle biopsy. Primary pancreatic neoplasm is an important differential for MCC metastatic to pancreas, especially with isolated pancreatic involvement.[17] EUS-guided FNA is a minimally invasive technique that enables preoperative diagnosis of primary and secondary pancreatic tumors.[1] Immunohistochemical staining is crucial in differentiating MCC from other cancers, such as small cell carcinoma, lymphoma, or melanoma, which may appear similar on routine histological staining.[1,13] Neuroendocrine markers, such as synaptophysin, chromogranin, and CD56, usually stain positive in MCC.

Including our patient, we found a total of 34 cases of MCC in literature with pancreatic metastasis (summarized in Table 1).[1,7,8,17-40] The mean age was 65 years (range of 42-87

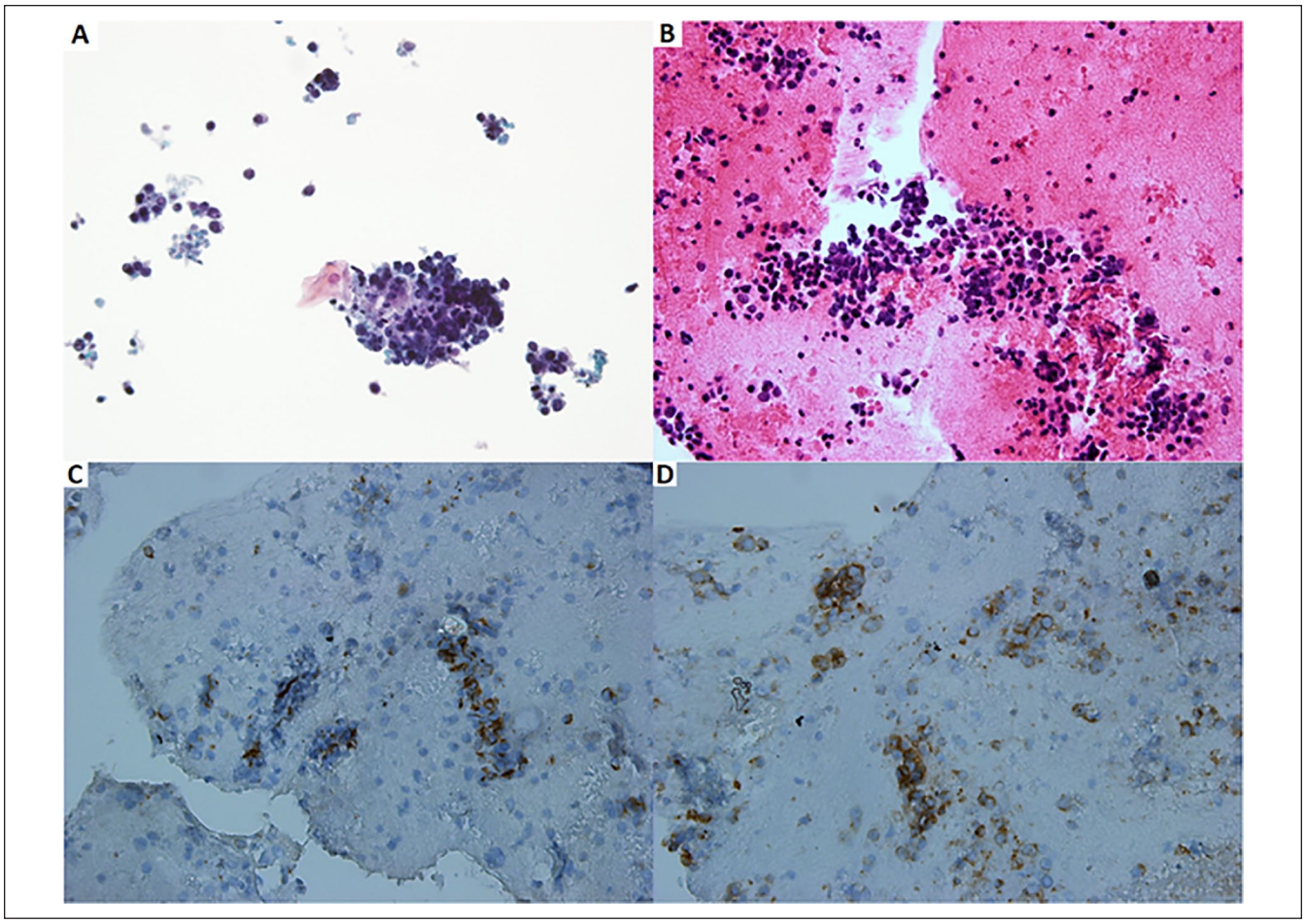

Figure 2. Endoscopic ultrasound-fine needle aspiration of head of pancreas. Malignant cells (A and B) in a necrotic background. Tumor cells show staining for synaptophysin (C) and CK-20 (D), consistent with patient's history of Merkel cell carcinoma.

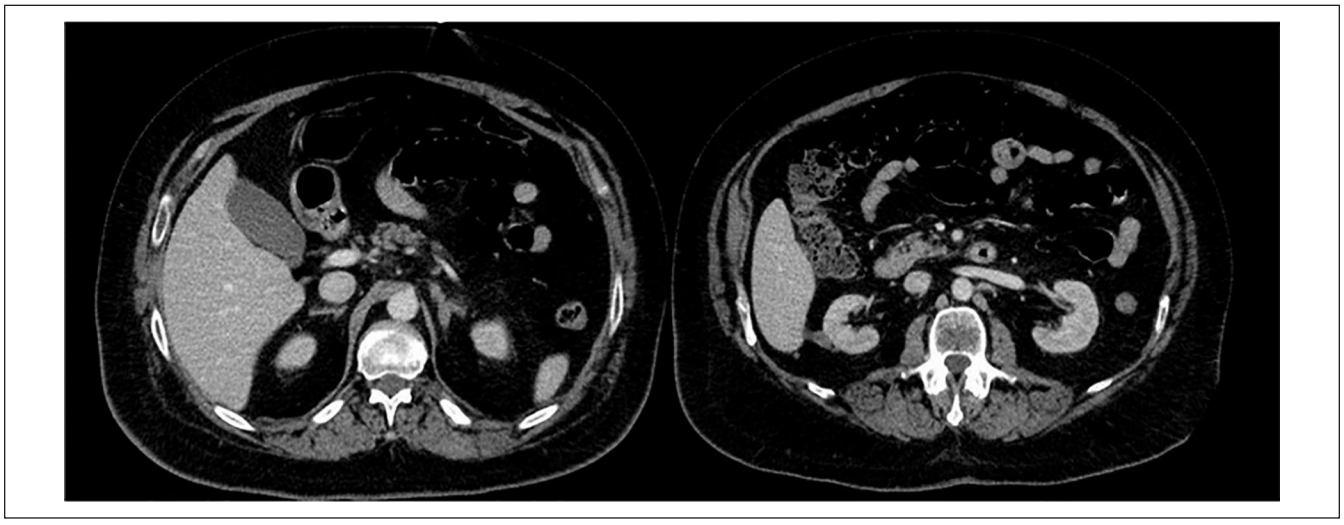

Figure 3. Computed tomography abdomen with contrast, 3 months post-chemotherapy. Resolution of previously noted masses and lymphadenopathy.

Table 1. Cases of Merkel Cell Carcinoma Metastatic to Pancreas.

Case	Age (years)	Sex	Primary site	Method of diagnosis	Treatment received	Interval between diagnosis of MCC and pancreatic metastasis (in months)	Interval between pancreatic metastasis and death (in months)
Safadi et al[18]	69	Female	Olecranon	Autopsy	None	24	0
Bachmeyer et al[19]	57	Male	Left eyelid	Surgical pathology	Surgical resection of pancreatic cyst	6	3
Ouellette et al[20]	64	Male	Right fifth digit	Surgical pathology	Pancreaticoduodenectomy and postoperative adjuvant RT. Progression of disease managed with salvage chemotherapy	48	24
Bachmann et al[21]	82	Female	Right eyebrow	Surgical pathology	Distal pancreatectomy, splenectomy, adrenalectomy along with resection of the splenic flexure of the colon	24	NA
Jessup et al[22]	53	Male	Left ankle	EUS-FNA	Chemotherapy	23	5
Hizawa et al[23]	85	Female	Right eyelid	Autopsy	None	20	2
Patel et al[24]	65	Male	Right gluteal region	CT and ERCP	ERCP-stent placement and chemo-RT	10	Alive at 6 months follow-up
Dim et al[25]	79	Female	Upper extremity	EUS-FNA	NA	15	NA
Krejčí et al[26]	54	Male	Right gluteal region	CT and PET-CT	Excision and radical re-excision of tumor followed by doxorubicin + cyclophosphamide	4	5
Bernstein et al[17]	56	Male	Left thigh	EUS-FNA	Cisplatin + etoposide with concurrent RT	6	NA
Vernadakis et al[27]	67	Female	Left forearm	Surgical pathology	Extended distal pancreatectomy, splenectomy with resection of splenic flexure of colon	30	Alive at 2-year follow-up
Bhardwaj et al[7]	62	Female	Dorsum of right hand	Percutaneous trans-hepatic biopsy	Palliative	108	2
Manatsathit et al[28]	65	Male	Left forearm	EUS-FNA	RT and concurrent chemotherapy	24	7
Ghouri et al[1]	51	Male	Right inguinal	EUS-FNA	Investigational chemotherapy and hyperthermia	30	12
	70	Male	Medial canthus of eye	EUS-FNA	Etoposide and carboplatin	33	9
	74	Male	Scalp	CT	Sirolimus and hydroxychloroquine, followed by etoposide and carboplatin	32	6
	70	Male	Right inguinal	PET-CT	Palliative	20	5
De Cock et al[29]	81	Female	Neck	Ultrasound-guided transabdominal biopsy	NA	12	NA
Kartal et al[30]	59	Female	Left gluteal region	Surgical pathology	Whipple procedure followed by cisplatin and etoposide	7	Alive at 30-month follow-up
Mantripragada et al[31]	42	Male	Unknown	Ultrasound-guided biopsy of pancreas	Nivolumab	12	Alive after 4 cycles of nivolumab
De Paredes et al[32]	75	Male	Right forearm	EUS-FNA	Carboplatin and etoposide	12	NA
Yaramada et al[33]	85	Male	Unknown	EUS-FNA	Carboplatin and etoposide followed by hospice care		NA
Maimone et al[34]	73	Male	Left elbow	EUS-FNA	NA	7	NA
Stoos-Veic et al[35]	52	Male	Right gluteus	EUS-FNA	NA	7	NA
	87	Male	Unknown	EUS-FNA	Palliative/supportive	30	NA
Lucci et al[9]	75	Male	Gluteal skin	EUS-FNA	NA		NA
Pinho et al[36]	71	Male	Left thigh	EUS-FNA	Cisplatin and etoposide	18	Alive at 6-month follow-up
Li et al[37]	33	Male	Unknown	EUS-FNA	Carboplatin and etoposide followed by pembrolizumab and palliative RT to axilla	0	Progressed after 6 months
Tarabadkar et al[38]	58	Male	Left calf	NA	Carboplatin and etoposide	NA	NA
	65	Male	Unknown	NA	Radiation and depot octreotide acetate injections	NA	NA
	61	Male	Right lower back	NA	Carboplatin and etoposide, followed by topotecan, followed by RT, followed by pazopanib	NA	NA
Zaremba et al[39]	61	Female	Right gluteal region	Biopsy? Of pancreas	Pembrolizumab X 27 doses	6	Alive at 15-month follow-up
Elkafrawy et al[40]	67	Male	Right eyebrow	PET-CT	Hospice	21	1.5
Current case	53	Male	Anterior chest	EUS-FNA	Cisplatin and etoposide	3	5

Abbreviations: MCC, Merkel cell carcinoma; RT, radiation therapy; EUS-FNA, endoscopic ultrasound-fine needle aspiration; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; NA, not available; PET, positron emission tomography.

years) and 74% were men. The mean duration from previous detectable MCC to development of pancreatic involvement was 20 months (range 0-108 months). Survival after diagnosis of pancreatic metastasis was highly variable and ranged from 0 to 30 months. Common presenting symptoms included abdominal pain/discomfort, abdominal mass, jaundice, and weight loss. Other patients were asymptomatic and were found to have an incidental pancreatic mass on imaging. Two cases were diagnosed at autopsy and 5 on surgical pathology. EUS-FNA was the most common diagnostic tool employed to diagnose metastatic MCC to pancreas and was used in 15 patients. Three patients were diagnosed with percutaneous/ultrasound-guided biopsy. Imaging with CT and/or positron emission tomography-CT was the sole means of diagnosis in 5 patients. Recurrence of MCC, manifesting with isolated pancreatic involvement is rare and has been described in 5 case reports.[7,19,20,25,28]

There are no guidelines specific to the management of pancreatic metastases of MCC. Checkpoint inhibitor immunotherapy is now the preferred initial treatment modality for metastatic MCC.[41] Although there are no randomized trials demonstrating the superiority of checkpoint immunotherapy compared with chemotherapy, immunotherapies provide response rates similar to those previously reported for chemotherapy and may provide greater durability of response.[41] Avelumab, an anti-PD-L1 (programmed death-ligand 1) agent, and anti-PD-1 (programmed cell death protein 1) agents nivolumab and pembrolizumab are used in this setting. Nivolumab was successfully used in a case of MCC metastatic to heart and pancreas, with a marked reduction in tumor burden after 4 cycles.[31] Zaremba et al[39] reported a patient who was treated with 27 cycles of pembrolizumab, with complete resolution of the pancreatic lesion which was sustained at 15 months of follow-up. Elkafrawy et al[40] reported a patient who developed new pancreatic lesions while on atezolizumab (PD-L1 inhibitor). The use of immune checkpoint inhibitors as neoadjuvant was studied recently. Nivolumab administered approximately 4 weeks before surgery in MCC-induced pathologic complete response and radiographic tumor regressions in approximately one-half of treated patients.[42] Ipilimumab is an anticytotoxic T-lymphocyte-associated antigen-4 agent. One study evaluated its utility among 13 patients who progressed through PD-1/PD-L1 inhibitors. An objective response was seen in 31% of patients.[43]

Chemotherapy is an option in patients with contraindication to immunotherapy.[41] Historically, most patients with pancreatic lesions were treated with chemotherapy. A combination of etoposide and platinum-based therapy was the most common regimen. MCC is a chemosensitive tumor with initial response rates of 60% to 70%,[4] although the responses are not durable[6] and clinical benefit on overall survival is unclear.[41] The median duration of response to chemotherapy ranges from 2 to 9 months.[6] Ghouri et al[1] reported 2 cases of MCC involving pancreas treated with a combination of etoposide and carboplatin, both with poor response. Others have reported favorable results with etoposide and platinum-based chemotherapy.[17,36]

Surgery may be beneficial in highly selective circumstances for resection of oligometastatic or symptomatic lesions.[41] Surgery with or without adjuvant chemotherapy and/or radiation therapy was performed in 6 cases. None of them underwent EUS before surgery. Most of the recently published cases were diagnosed with EUS-FNA due to the increase in the availability of this diagnostic modality. It is interesting to note that the 3 patients with the longest survival at follow-up underwent surgery.

There is evidence that MCC tumors express angiogenesis factors, such as vascular endothelial growth factor. Tarabadkar et al[38] reported a longer duration of benefit with vascular endothelial growth factor receptor tyrosine kinase inhibitors, compared with prior chemotherapy regimens in a case series of 5 patients. Other molecular targets being evaluated for MCC include phosphoinositide 3-kinase inhibitors and poly ADP [adenosine diphosphate]-ribose polymerase inhibitors.[44]

Conclusion

Pancreatic involvement by MCC is rare and usually occurs along with involvement of other abdominal organs. It is not possible to differentiate MCC from primary pancreatic tumors with imaging alone, and biopsy with immunohistochemistry analysis is vital in establishing the correct diagnosis. Therapeutic modalities include immunotherapy, chemotherapy, and potentially surgery in very selected cases with oligometastatic disease. Newer targets of therapy are currently under investigation.

Author's Note

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The article has been submitted solely to this journal and is not published, in press, or submitted elsewhere.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases.

Informed Consent

Informed consent was not obtained because the patient passed away and we were not able to reach the family.

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