

## CASE REPORT

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# Epithelioid sarcoma-like epithelioid hemangioendothelioma of the small bowel: A case report and review of literature

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## ABSTRACT

We describe the case of a 71-year-old male patient with a polypoid neof ormation that was situated in the submucosa of the small intestine. Morphologically it was epithelioid type, with an immunophenotypic profile showing some features of the epithelioid sarcoma and with others of the hemangioendothelioma.

**Keywords:** Epithelioid hemangioendothelioma, Epithelioid sarcoma, Immunohistochemistry

### How to cite this article

Filotico M, Africa G, Floccari F, D'Amuri A. Epithelioid sarcoma-like epithelioid hemangioendothelioma of the small bowel: A case report and review of literature. J Case Rep Images Pathol 2020;6:100033Z11MF2020.

Article ID: 100033Z11MF2020

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doi: 10.5348/100033Z11MF2020CR

## INTRODUCTION

Epithelioid sarcoma (ES) [1] is a malignant mesenchymal neoplasm that exhibits epithelioid cytomorphology and a predominantly epithelial phenotype occurring in pediatric and adult populations with an unpredictable course and better prognosis in pediatric patients. There are two typical morphologies, including classic type with epithelioid to spindled cells with central pseudogranulomatous architecture, and proximal type with predominant epithelioid and rhabdoid cells. At immunohistochemistry, cells are positive for pancytokeratin and lost INI1, while to submit molecular mutations in INI1/SMARCB1. Either type may arise anywhere. The classic type is usually distal upper extremity, >60% arising in the fingers and hand, whereas the proximal type is more common in deep soft tissue, truncal tissue (e.g., pelvic peritoneal, genital, and inguinal), and buttock/hip.

Epithelioid hemangioendothelioma (EHE) [1] is an intermediate grade vascular malignancy that is closely associated with or arising from a vein in 50% of cases, usually adults with 60% of women. The sites are extremities (60%) and also head and neck, mediastinum, and trunk. It is an unpredictable clinical course, but less aggressive than angiosarcoma. About 13% of cases recur, 20–30% metastasize (lung and lymph nodes), 13% die of disease for lung, mortality is 65%. High risk (>3 MF/50 HPF and size >3 cm) has five years disease specific survival of 59% versus 100% for low risk. Microscopic description shows cords or small nests of round endothelial cells with abundant eosinophilic cytoplasm. Tumors arising from vessels extend outward from the lumen toward soft tissue and tumor cells often have intracytoplasmic vacuoles representing small vascular lumina, which may resemble mucin. Nuclei are round and may be indented and usually minimal mitotic activity, atypia or necrosis, but 25% of cases exhibit frank malignant features of prominent nuclear pleomorphism, mitotic activity, focal spindling, or necrosis with stroma may be scanty or myxoid. This description may have peripheral inflammatory infiltrate with germinal centers and eosinophils, multinucleated giant cells. At immunohistochemistry, tumor cells are positive for vimentin, CD31, anti-factor VIII, keratin, and reticulin.

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Received: 30 March 2020

Accepted: 13 April 2020

Published: 24 April 2020

Pseudomyogenic hemangioendothelioma [1] is rarely metastasizing vascular tumor with histology mimicking a myoid tumor or ES locally aggressive but rarely metastasizing vascular tumor occurring most commonly in young adults <40 years old. The histology findings are fascicles or sheets of plump spindled to epithelioid cells with bright eosinophilic cytoplasm. At immunohistochemistry, tumor cells are: keratin+, ERG+, FLI1+, CD31+, FOSB+, CAMTA1-, and INI1 retained; and molecular cell is: t(7;19)*SERPINE1-FOSB*. Most common locations are the lower extremities like lower limbs: 54%, upper limbs: 24%, trunk: 18%, head and neck: 4%. Approximately 67% of reported cases are often multifocal. The affected tissues are: dermis (31%), subcutaneous tissue (20%), muscle (34%), and bone (14%).

Epithelioid sarcoma-like epithelioid hemangioendothelioma (ES-H) [1] is a low-grade vascular tumor that closely mimics an ES because of growth in solid sheets and nests, the eosinophilia of the rounded to slightly spindled neoplastic cells, and the diffuse, strong cytokeratin expression. The tumors were characterized by sheets, ill-defined nodules, or fascicles of deeply eosinophilic cells set within a desmoplastic stroma. Multicellular vascular channel formation and/or hemorrhage were absent in all cases. In some cases intracytoplasmic vacuolization suggestive of intracytoplasmic vascular lumen formation was noted. The typical neoplastic cell was large and rounded in shape but modulated in areas to a spindled or multipolar shape. Mitotic activity was low (<5 mitotic figures/50 high power fields), nuclear pleomorphism was mild to moderate, and necrosis was absent. The tumors were positive for cytokeratin, vimentin, CD31, FLI-1, but negative for CD34. Epithelioid sarcoma-like hemangioendothelioma appears to be a largely unrecognized epithelioid vascular tumor with an indolent course. Despite its similar clinical and histologic features, it differs from ES by the presence of endothelial markers and the absence to date of distant metastases. Its distinction from other epithelioid vascular lesions is discussed. This tumor fits best into the family of “*hemangioendothelioma*” or vascular lesions of intermediate malignancy. Epithelioid sarcoma-like hemangioendothelioma represents a rare morphologic type of hemangioendothelioma. It has some overlapping histologic features with ES and EHE. The endothelial nature of ES-H is difficult to be verified on the basis of morphologic examination alone. Confirmation of the diagnosis with immunohistochemistry is necessary. Epithelioid sarcoma-like hemangioendothelioma is likely related to EHE and may represent a cellular spindle cell variant of EHE.

We describe the case of a 71-year-old male patient with a polypoid neformation that was located in the submucosa of the small intestine. Morphologically it was epithelioid type, with an immunophenotypic profile showing some features of the ES and with others of the hemangioendothelioma. The finding of an epithelioid tumor in the context of the small bowel submucosa,

with a very particular immunohistochemical that is distinguished from the most common diagnostic options for these types of tumors made the case worthy of further investigation.

## CASE REPORT

A 71-year-old male patient was hospitalized due to an intestinal occlusive syndrome, with an unknown clinical history. Computed tomography (CT) scan showed ectasia of jejuno-ileal loops with sudden obstruction of the downstream lumen. Invagination at the jejunal level caused by a massive intraluminal polyp was found at surgery. The stretch of ileal loop is resected to embody the polyp. The surgical specimen was fixed in formalin and embedded in paraffin. The sections were then stained with hematoxylin and eosin. Grossly the lesions appear like a dome-shaped neof ormation, with a broad base of dimensions of 3 × 2 cm, partially ulcerated on the surface of a pinkish color. At histology the polypoid neof ormation is covered on the surface by a mucosa of the small intestine that is widely ulcerated (Figure 1A). Beneath lies an intact muscularis mucosae, which represents a solid neoplastic growth (Figure 1B). It consists of epitheliomorph ic elements of globose-polyhedral shape with large, amphophilic cytoplasm and bulky vesicular nucleus. No mitotic activity was found. The elements tend to aggregate in hepatoid-like trabeculae (Figure 1C and D) or give rise to mazy cavities wherein they project papillary-like vegetations with hobnail nuclei (Figure 2). Intracytoplasmic lumens are sporadically found as well (Figure 1D, arrow). With immunohistochemistry, a large

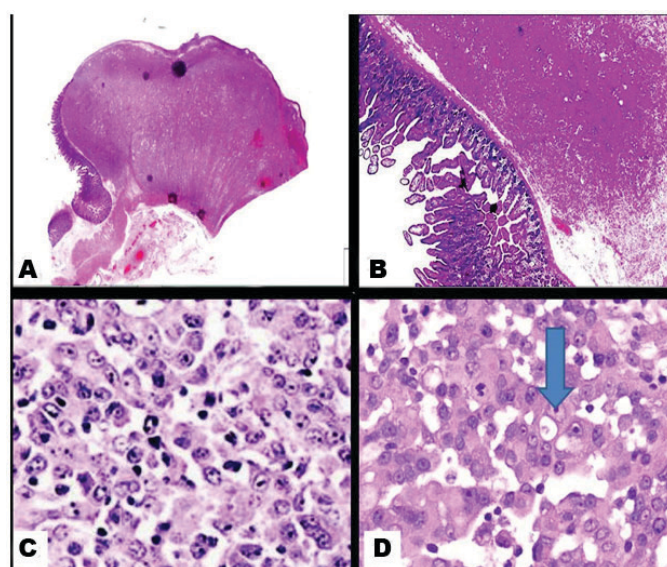


Figure 1: (A) Polypoid neof ormation partially covered by mucosa of the small bowel type, extensively ulcerated (HE 20×). (B) The core of the polyp comprises of a compact tissue that is located beneath the muscle mucosae (HE 120×). (C) Proliferation consists of epithelioid elements arranged in trabeculae (HE 250×). (D) Intracytoplasmic lumens are recognized sporadically (arrow) (HE 250×).

panel of antibodies is tested and the results are: CKAE1/AE3+, MNF116+, vimentin +, EMA+, Ca125+, CD10+ focally, CD31+, FLI1+, INI1+, CD34-, chromogranin-, synaptophysin-, CD117-, S100-, desmin-, myogenin- (Figures 3A–D to 5A–D). The final diagnosis of ES-H of the small bowel was posed.

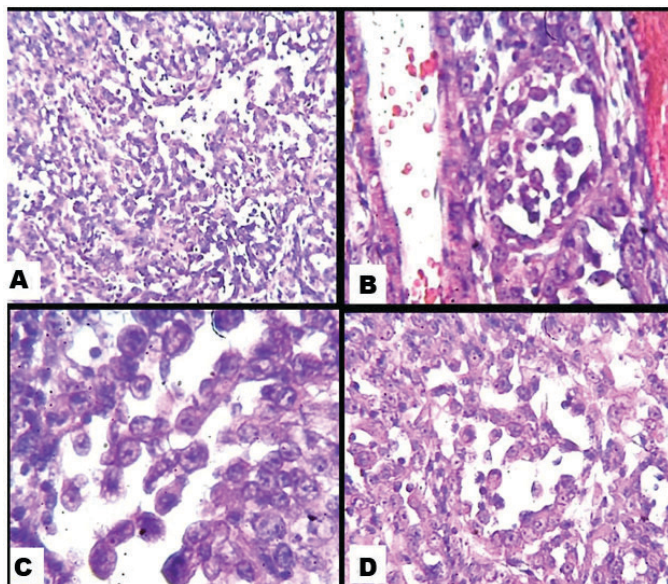


Figure 2: (A)–(D) In some areas, the proliferation assumes a mazy configuration with pseudopapillary intraluminal vegetation covered with hobnail-like elements (HE 250×).

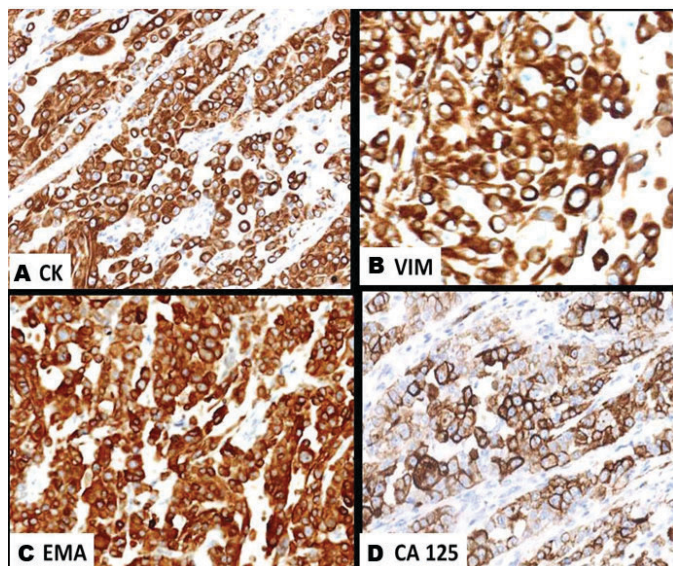


Figure 3: (A) CKAE1/AE3; (B) Vimentin; (C) EMA; (D) CA125 (250×).

## DISCUSSION

The diagnostic workup of this case was very devious as necessitated the consideration of a large number of different options. The trabecular epithelioid morphology of loosely hepatoid aspect was found to be oriented toward a repetitive process by a hepatic primitiveness. No

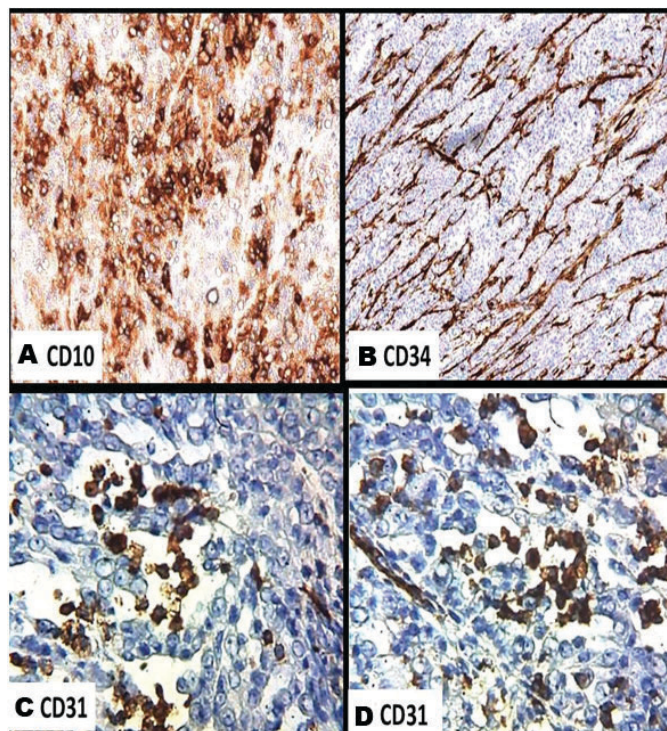


Figure 4: (A) CD10; (B) CD34; (C), (D) CD31 (250×).

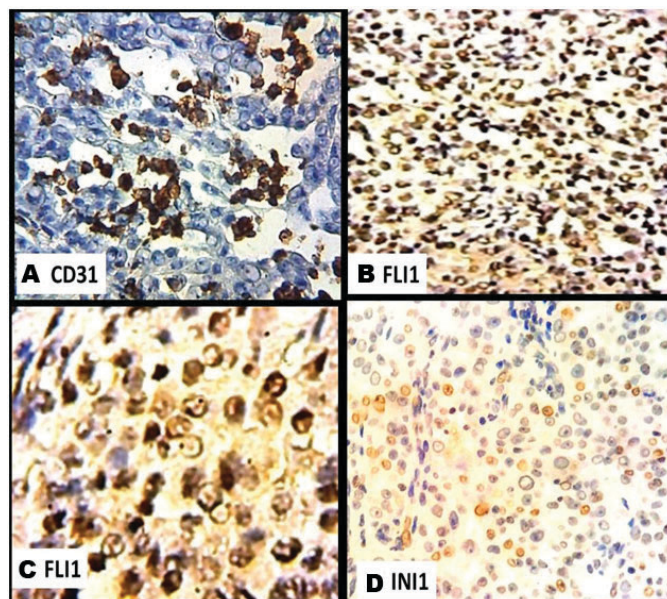


Figure 5: (A) CD31; (B), (C) FLI1; (D) INI1 (250×).

clinical objective or instrumental finding comforted this hypothesis, which was also denied later on by the negativity of the hepatocyte antibody. Immunohistochemical investigation revealed an intense, widespread positivity for epithelial markers (CKAE1/AE3, MNF116, EMA; Figure 3A–D), associated with an equally widespread and intense positivity for vimentin. Also positive tumor cells were CD31, CD10, Ca125, FLI1, and INI1 preserved (Table 1, Figures 4A–D to 5A–D). Based on the aforementioned data, the differential diagnosis was oriented into two entities: ES and EHE. With the identification of ES in

Table 1: Immunohistochemical profile of epithelioid sarcoma (ES), epithelioid hemangioendothelioma (EHE), and epithelioid sarcoma-like hemangioendothelioma (ES-H)

Antibody	ES	EHE	ES-H
CKAE1/AE3	+	+ (31%)	+
CKMNF116	+	*ND	+
EMA	+	-	+
*Vim	+	+ (100%)	+
ERG	+	+ (81%)	*ND
FLI1	-	+ (100%)	+
CD40	*ND	+ (71%)	*ND
Ca125	+	-	+
CD31	-	+ (100%)	+
CD34	+ (50%)	+ (81%)	-
INI1	- loss	+ *ret	+ *ret
TF3	*ND	+ (88%)	*ND
CD10	*ND	+	+
*SMA	-/+	-	-
Desmin	-	-	-
Myogenin	-	*ND	*ND
S100	-	-	-
CD117	-	-	-
HMB45	-	-	*ND

\*Abbreviations: ND: not determined; Vim: vimentin; ret: retained; SMA: smooth actin.

1970, a controversial and unfinished chapter was seen in the surgical pathology of soft tissue tumors [2]. While a well-defined histogenesis is recognized in non-visceral epithelioid neoplasms for the most part (muscular, vascular, Schwannian, etc.) for ES, a precise histogenesis has not yet been indicated so much so that even 50 years after its first presentation, and despite the constant advances in immunohistochemistry and molecular biology, it is still classified among neoplasms of uncertain differentiation. The early immunohistochemical investigations on this tumor highlighted a remarkable characteristic of the widespread expressivity of CK and vimentin [3]. In subsequent studies, positivity for EMA (40–95%) and CD34 (50%) [4], Ca125 (Table 1) [5, 6], and the loss of INI1 has been reported (Table 1) [7]. A particular mention needs to be made about the latter aspect in consideration of a very reliable marker for the ES diagnosis. In appropriate contexts, expressivity is reported for ERG in 38% of the ES [8] and FLI1 is consistently negative (Table 1) [9].

The EHE was described in 1982 by Weiss and Enzinger who defined morphological characteristics as follows: “They are composed of rounded or slightly spindled eosinophilic endothelial cells with rounded nuclei and prominent cytoplasmic vacuolization. The latter feature probably represents primitive lumen formation by a

single cell. The cells grown in small nests or cords and only focally line well-formed vascular channels. The pattern of solid growth and the epithelioid appearance of the endothelium frequently leads to the mistaken diagnosis of metastatic carcinoma” [10]. Based on the most recent research, the immunophenotypic profile of this neoplasm can be summarized as follows: ERG +(100%), CD31+(100%), CD34+(81%), FLI1+(100%), CD40+(71%), CK18+(25%), pankeratin +(31%), EMA-, IN1 preserved, SMACT+(10% focal), TF3+ (88%), CD10 +(78%) (Table 1) [11]. The case study shares the following positivity with ES: CK, Vim, EMA, Ca125, whereas does not agree the positivity for SMA (Table 1). However, it presents the negativity for desmin, myogenin, S100, and CD117 (Table 1). It shares the following positivity with EHE: CK, vimentin, FLI1, CD31, INI1ret, and CD10, while the positivity is also not shared for CD34 (Table 1). This indiscrimination of morphological and immunophenotypic expression is not new for these types of lesions [12]. In 1992, Mirra, for a spindle-cell neoplasm expressing CK and Vim, created the oxymoron “*Fibroma like Epithelioid Sarcoma*” [13]. In a series (2003) of 95 cases, 7 seven were reported under this name [14]. In another study conducted on 7 cases (2003), negativity for CD34, expression of FLI1 and INI preserved was highlighted.

The authors labeled this lesion as ES-H [15]. An additional study of 50 cases (2011) substantially confirmed the previous report by changing its name to pseudomyogenic hemangioendothelioma (PMHE). The name was officially adopted for this type of lesion [16]. The immunophenotypic variability of this type of injury is not limited to what has been described above. In fact, other reports have appeared in extant literature as well. Another entity was described with similar morphologic pattern and with a distinctive immunophenotypic profile: CK+, vimentin+, CD34+, Ki-67 < 1%, FLI1- and INI1-retained, and has been labeled as superficial CD34-positive fibroblastic tumor [17]. In the same period, Filotico et al. reported a case with immunophenotypic profile: CK+, vimentin+, CD34+, CD31+, FLI1+, INI1-retained [18]. Notably, all these lesions are characterized by an indolent course with some rare recurrences. The case studied above shows an epithelioid morphology that is close to that of proximal type ES and expresses some antigens characteristic of this neoplasm, such as the intense positivity for cytokeratins, vimentin, and EMA, associated with Ca125. However, for this neoplasm, it differs by the conservation of INI1. In addition, it contemporarily expresses characteristic antigens of EHE, such as FLI1, CD31, and CD10. With PMHE, it shares the negativity for CD34 (Table 1).

## CONCLUSION

This case, which could be called ES-H, adds another element to that kaleidoscopic group of lesions that are

immunophenotypically placed between the classic ES and the classic EHE. Additionally, it suggests that there may be some genotypic link between these two entities that these hybrid lesions would bear witness too. The uniqueness of this case disallowed predictions being made about its biological behavior.

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## Acknowledgments

The authors are grateful to Dr. Antonina Parafioriti, Institute Gaetano Pini, Milan (Italy) and Dr. Francesco Alfredo Zito, Cancer Institute, John Paul II, Bari (Italy) for the collaboration provided in the study of this case.

## Author Contributions

Marcello Filotico – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Giovanni Africa – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Federica Floccari – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Alessandro D'Amuri – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

## Guarantor of Submission

The corresponding author is the guarantor of submission.

**Source of Support**

None.

**Consent Statement**

Written informed consent was obtained from the patient for publication of this article.

**Conflict of Interest**

Authors declare no conflict of interest.

**Data Availability**

All relevant data are within the paper and its Supporting Information files.

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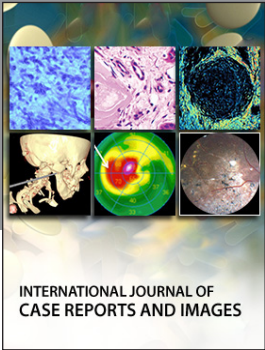
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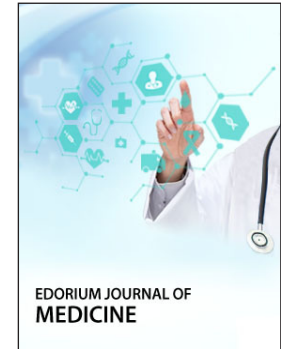
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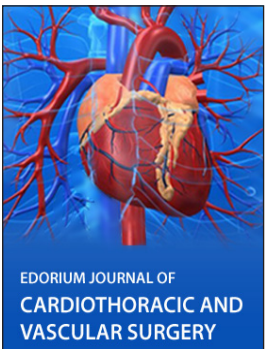
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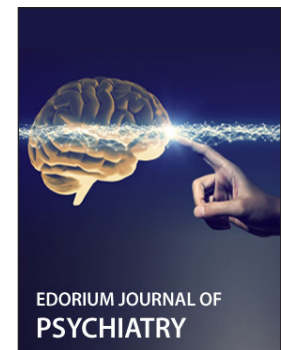
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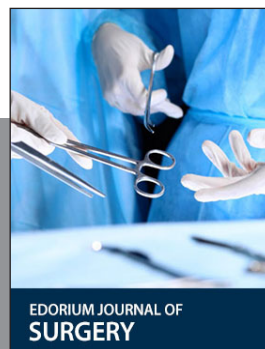
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