Large Cell Neuroendocrine Tumor of Gallbladder: A Case Report and Review of the Literature

Safra Kesesinin Büyük Hücreli Nöroendokrin Karsinomu: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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ABSTRACT Neuroendocrine gastroenteropancreatic tumors (GEP-NET) constitute a heterogeneous group of tumors with their origin in neuroendocrine cells of the embryological gut, most commonly with the primary lesion located in the gastric mucosa, the small and large intestine, the rectum or the pancreas. However, neuroendocrine tumors are rarely localized in gallbladder. There were ten case reports published in English literature. Four of them were mixed tumors with adenocarcinomas, and the other three were pure large cell neuroendocrine tumors (LCNET). Histopathologic subtype was unspecified at three of them. We present the fourth case of pure LCNET of gallbladder. A 76 years-old man was admitted to the hospital with dyspepsia. A tumor was detected in the gallbladder. Cholecystectomy and hepatic resection were performed. Pathologic evaluation revealed weak differentiated LCNET. Immediately after four cycles of adjuvant chemotherapy, local relapse developed. Patient died 16 months after diagnosis due to hepatic insufficiency related to multiple hepatic metastases. LCNET in the gallbladder is a very rare entity and has a poor prognosis. In literature, the median survival of the patients with pure LCNET of gallbladder ranges between 1 and 14 months, whereas mixed tumors have longer survival.

Key Words: Carcinoma, large cell; gallbladder; gastro-enteropancreatic neuroendocrine tumor

ÖZET Nöroendokrin gastroenteropankreatik tümörleri (GEP-NET) primer olarak çoklukla gastrik mukoza, ince ve kalın barsaklar, pankreas veya rektumdaki primer lezyonlardan ve embriyolojik barsaktaki nöroendokrin tümörlerden köken alan heterojen özellikte bir grup malignitelerdir. Ancak, safra kesesine lokalize nöroendokrin tümörler oldukça nadirdir. Literatürde bugüne kadar safra kesesine lokalize 10 büyük hücreli nöroendokrin karsinom (BHNK) vakası bildirilmiştir. Bu olguların dördü adenokarsinom ile mikst, üçüde saf BHNK'dur. Olguların üçünde histopatolojik alt tip belirtilmemiştir. Bu olgu sunumunda, literatürdeki dördüncü saf primer safra kesesi BHNK vakası bildirilmektedir. Yetmiş-altı yaşında erkek hasta hazımsızlık yakınması ile hastanemize başvurdu. Safra kesesinde bir tümör saptandı. Kolesistektomi ve karaciğer rezeksiyonu yapıldı. Patolojik inceleme az diferansiye BHNK ile uyumlu bulundu. Adjuvan dört kür kemoterapiden hemen sonra lokal nüks saptandı. Hasta tanısından 16 ay sonra multipl karaciğer metastazlarına bağlı hepatik yetmezlik nedeniyle öldü. Safra kesesine lokalize saf BHNK çok nadir görülür ve kötü bir klinik seyir gösterir. Literatürde tanımlanan saf BHNK olgularında sağkalım süreleri 1-14 ay arasında bildirilmişken, mikst olgularda sağkalım daha uzundur.

Anahtar Kelimeler: Karsinom, büyük hücreli; safra kesesi;
gastro-enteropankreatik nöroendokrin tümör

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Neuroendocrine tumors (NETs) are histologically varied entities and can range from indolent, unrecognized neoplasms to highly active, metastatic secretory tumors.[1] Tumors localized in the gall-

bladder are mainly adenocarcinomas, but numerous other types, including squamous cell carcinoma, adenosquamous carcinoma and sarcoma have been documented.[2,3] Although more than 60% of (NET) arise in gastrointestinal system, gallbladder is one of the unusual locations for extrapulmonar high-grade neuroendocrine carcinoma.[4] According to American epidemiological data; gallbladder NETs are representing only 0.2% of all NETs.[5] The primary NET of gall-bladder mainly consists of carcinoid tumors and small-cell carcinomas.[6] Primary large cell neuroendocrine tumor (LCNET) of gallbladder is extremely rare and only 10 cases has been described in the literature.[7-14] Histologic subtypes were unspecified at three of 10 cases.[12-14] Four of them were mixed tumors with adenocarcinomas, and the other three cases were pure LCNET.[7-11] We report the fourth case of pure LCNET of gallbladder.

CASE REPORT

A 76-year-old man was admitted to the hospital with dyspepsia. A CT scan showed a contrast-enhancing lobulated mass of 1.5 cm in the neck region of gallbladder. There was no regional and distant lymph node enlargement. Routine laboratory tests performed on admission were unremarkable. The patient underwent cholecystectomy and hepatic bed resection. Histopathological examination revealed poorly differentiated large cell neuroendocrine carcinoma (Figure 1,2). The tumor was 2 cm in diameter, invaded the muscular layer and extended into the serosa, but not perforated serosa. There was no involvement of liver. Intestinal metaplasia was present in the mucosa adjacent to the tumor. Lymphovascular and perineural invasion were identified. Pan-cytokeratin was diffusely positive. Immunohistochemically, the tumor cells demonstrated staining with synaptophysin and chromogranin-A (Figure 3). The Ki-67 immunostain showed a proliferative rate of 90%.

Postoperative staging with positron emission tomography showed no uptake of F18-fluorodeoxyglucose. Patient was staged as T2NxM0 (stage II), according to AJCC 7th edition. He received four cycles of adjuvant chemotherapy consisting of cisplatin and etoposide. The patient had local recurrence immediately after the completion of adjuvant chemotherapy, i.e. 4 months after the initial diagnosis. He received one cycle of cyclophosphamide-adriamycin-vincristine combination chemotherapy and 3 cycles of gemcitabine, consecutively. No response was seen with these therapies. Chemoradiation with capecitabine was initiated, but stopped early due to the development of multi-

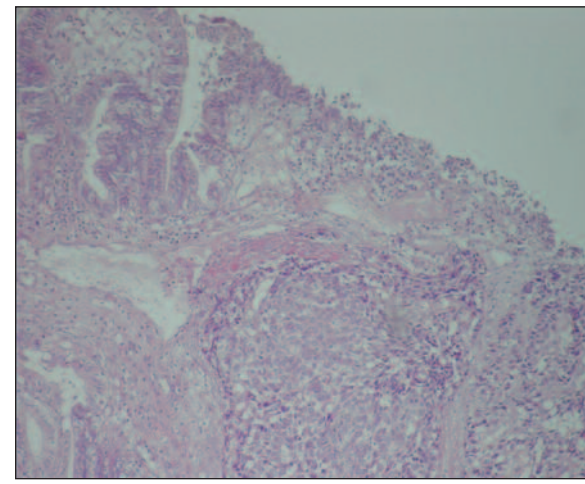

FIGURE 1: Invasive high-grade neuroendocrine neoplasm showing epithelioid features with necrosis and ulceration near the non-neoplastic mucosa of gall-bladder (Original magnification x40 Olympus BX 51 light microscope objectives; Hematoxylin & Eosin).
(See color figure at http://www.turkiyeklinikleri.com/journal/turkiye-klinikleri-journal-of-case-reports/1300-0284/tr-index.html)

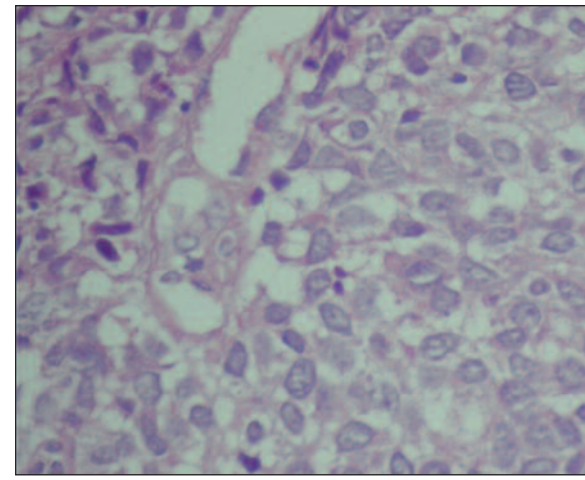

FIGURE 2: Tumor consists of middle-large nucleated neoplastic cells with fine granulated chromatin and apparent nucleoli, showing mitotic figures (overall 15 mitosis/10 high power field; original magnification x 100 Olympus BX 51 light microscope objectives, Hematoxylin & Eosin).
(See color figure at http://www.turkiyeklinikleri.com/journal/turkiye-klinikleri-journal-of-case-reports/1300-0284/tr-index.html)

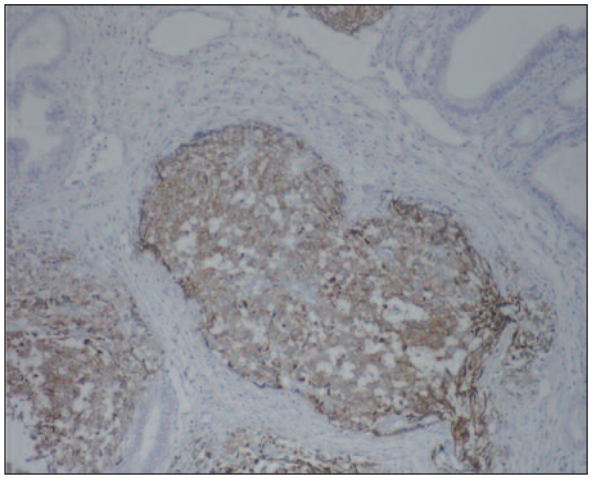

FIGURE 3: Immunohistochemical studies revealed diffuse synaptophysin expression (Original magnification x40 Olympus BX 51 light microscope objectives).

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ple liver metastases. He received three cycles of metronomic oral cyclophosphamide-etoposide chemotherapy with no response. The patient died 16 months after initial diagnosis due to liver failure.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

DISCUSSION

More than 90% of gallbladder cancers are adenocarcinoma. Neuroendocrine tumors of gallbladder are very rare and may occur as a pure form or mixed, most commonly with adenocarcinoma. LCNET has been reported in both pulmonary and extrapulmonary locations. In general, it represents an aggressive tumor type and shares the poor prognosis of small cell carcinoma, with a tendency for early lymph node and distant metastases.[7]

NETs are classified to three separate groups according to the World Health Organisation (WHO) 2010[15] as below;

1- Carcinoid (NET G1-carcinoid- NET G2, NEC G3- large cell and small cell type)

2- Mixed adenoneuroendocrine carcinoma (MANEC)

3- Hyperplastic and preneoplastic lesions

- NET, neuroendocrine tumor-well differentiated; NEC, neuroendocrine carcinoma-poorly differentiated; G, Grade

Within the gallbladder, the differential diagnosis of LCNET includes other poorly differentiated tumors, including adenocarcinomas, lymphomas, sarcomas and metastatic melanoma. Immunohistochemical studies easily distinguish between these entities. As with neuroendocrine tumors of other organs, the immunophenotype of LCNET of the gallbladder include positivity for pancytokeratin antibodies, NSE, synaptophysin, and chromogranin-A.[7,16]

The origin of neuroendocrine carcinomas of gallbladder is unclear. In contrast to other parts of the gastrointestinal tract, normal gallbladder mucosa does not contain neuroendocrine cells. However, neuroendocrine cells can be identified in association with intestinal metaplasia.[17,18] So, intestinal metaplasia can be the initial step in the development of the neuroendocrine carcinomas of gallbladder.[7] In the current case, intestinal metaplasia was present in the mucosa adjacent to the tumor. A second explanation is that a pluripotent stem cell or a progenitor cell can serve as a common precursor for adenocarcinoma and neuroendocrine tumors, including carcinoid, small cell and large cell neuroendocrine carcinomas.[19,20] This can yield pure neuroendocrine tumors or mixed tumors.

Due to rarity of LCNET of the gallbladder, there is no well-established treatment strategy. In patients with resectable tumors, aggressive surgery, including cholecystectomy, en bloc hepatic resection and lymphadenectomy with or without bile duct excision, which is similar to that performed in gallbladder adenocarcinoma, seems to be the mainstay of the treatment.[21] Although there is no data on the benefit of adjuvant chemotherapy, the general practice of four cycles of adjuvant chemotherapy in poorly differentiated neuroendocrine tumors of other organs can also be applied to LCNEC of gallbladder. Adjuvant chemotherapy with cisplatin and etoposide seems to be reasonable. Different ablative techniques such as ra-

diofrequency ablation, laser ablation and cryotherapy, can be used to control of regional liver metastases.[16] Other locoregional approaches include embolization of the hepatic artery by particles or cytotoxic agents (chemoembolization).[22]

For metastatic disease, chemotherapeutic agents active in poorly differentiated neuroendocrine tumors of other organs can be considered. Cytotoxic treatment has been of limited value for the treatment of low-proliferating gastroenteropancreatic neuroendocrine (GEP-NET) tumors (response rates: 10%-15%), but has been the standard of care for malignant endocrine pancreatic tumors (with response rates: 30%-50%). Poorly differentiated tumors are mostly treated with cisplatin/oxaliplatin plus etoposide (response rates: 40%-60%).[23,24] Somatostatin analogues and α-interferons has proven effective in the control of associated clinical syndromes related to hormone production and release (carcinoid syndrome, VIPoma and glucagonoma syndrome).[24] Their use in non-functioning tumours has been debated, but a recent study has indicated an antiproliferative effect by somatostatin analogues in both functioning and nonfunctioning tumours (the PROMID study).[25] A combination of somatostatin analogues and α-interferons has been effective in patients with resistance to either drug.[26] Additionally, α-interferon up-regulates the numbers of somatostatin receptor type 2.[27] Peptide receptor radiotherapy (PRRT) treatment is an option in patients who present with high-grade uptake on somatostatin receptor scintigraphy.[28] Recently antiangiogenic agents (bevacizumab, sunitinib) and m-TOR inhibitors (RAD001, everolimus) have been applied in GEP-NETs with objective response rates of 10%-20%.[24,29]

When the 11 cases of LCNET of gallbladder is reviewed (Table 1), female sex predilection was seen.[7-14] Median age of the patients was 65 years, similar to gallbladder adenocarcinoma. The disease course was very aggressive. All patients with pure LCNET died, while three of four patients with combined LCNET and adenocarcinoma were alive and in remission at the last follow-up. These three patients had only small foci of LCNET admixed with adenocarcinoma. Although it is not proper to draw conclusions from very limited data of 11 cases in the literature, it can be speculated that mixed tumors have better prognosis. The median survival was between 1-14 months in pure LCNET of gallbladder; however mixed tumors had longer median survival times in literature.

The aggressiveness and the poor prognosis of the LCNET of gallbladder in the presented case is in accordance with the previous reports. The poor prognosis is mainly due to diagnosis at an advanced stage in most cases. However, prognosis depends not only on the stage of the disease, but also on the histological type. Adenocarcinomas and other differentiated carcinomas are generally associated

TABLE 1: The features of large cell neuroendocrine tumors in gallbladder.

References	# cases	Age (years)	Sex	Stage at diagnosis	Types	Last status	Survival (months)
Papotti et al.[7]	2	65	M	pT2NxM0	Pure	Died	14 months (Pure)
		50	M	pT2NxM0	Mixed	Alive, in remission	+12 months (Mixed)
Jun et al.[8]	2	55	F	Metastatic	Pure	Died	1 month
		67	M	Metastatic	Pure	Died	10 months
Noske et al.[9]	1	81	F	Metastatic	Mixed	Died	6 months* (metastatic at diagnosis)
Oshiro et al.[10]	1	55	F	pT2N0M0	Mixed	Alive, in remission	+40 months*
Sato et al.[11]	1	68	F	pT3NxM0	Mixed	Alive, in remission	+12 months
Shimono et al.[12]	1	64	F	cT4N0M0	Unspecified	Died	69 months
Lin et al.[13]	1	65	F	Unspecified	Unspecified	Died	3 months
Yoon et al.[14]	1	38	F	Metastatic	Unspecified	Died	5 months
Our case	1	76	M	pT2NxM0	Pure	Died	16 months

* Survival data obtained by personal communication; F:Female; M: Male; p: Pathological staging; c: clinical staging.

with a relatively favorable prognosis when compared to small cell and large cell neuroendocrine carcinomas.[6,30] In cases of combined neuroendocrine cell carcinoma and adenocarcinoma, the prognosis depends on how advanced the neuroendocrine cell carcinoma is, because of more aggressive biologic behavior than adenocarcinoma.[31]

In conclusion, large cell neuroendocrine tumor of gallbladder has a poor outcome, even if it is diagnosed in early stage. Early diagnosis, prompt and appropriate surgical treatment can lead to better prognosis. The recognition of this rare tumor type carries important clinical implications in regard to the use of chemotherapeutic agents.

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