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A CASE REPORT OF GALLBLADDER CANCER IN A 17-YEAR-OLD PATIENT: DIAGNOSTIC CHALLENGES AND SURGICAL MANAGEMENT

ON YEDİ YAŞINDAKİ BİR HASTADA SAFRA KESESİ KANSERİ OLGUSU: TANISAL ZORLUKLAR VE CERRAHİ TEDAVİ

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ABSTRACT

Gallbladder cancer is a rare and aggressive malignancy with a poor prognosis, often diagnosed incidentally or at an advanced stage. This case study demonstrates an uncommon clinical entity of Gallbladder cancer in a 17-year-old male. The patient was presented with generalised abdominal pain and leukocytosis and mildly elevated liver enzymes. Initial imaging showed no gallstones; however, subsequent ultrasonography revealed an intraluminal hyperechoic lesion in the gallbladder. Laparoscopic cholecystectomy and biopsy confirmed well-differentiated adenocarcinoma without lymphovascular or perineural invasion. On follow-up, no complication was reported. In this case report, we highlight the importance of considering Gallbladder cancera differential diagnosis after excluding the most common aetiologies at the young age group.

Keywords: Gallbladder cancer, cancer, young age

ÖZET

Safra kesesi kanseri, genellikle tesadüfen veya ileri evrede teşhis edilen, kötü prognozlu nadir ve agresif bir malignitedir. Bu olgu sunumunda, 17 yaşında bir erkek hastada nadir görülen bir safra kesesi kanseri olgusu sunulmaktadır. Yaygın karın ağrısı, lökositoz ve karaciğer enzimlerinde hafif artış sebebiyle başvurmuştu. İlk yapılan görüntülemede safra kesesinde taş görülmedi ancak daha sonraki ultrasonografide safra kesesinde intraluminal hiperekoik bir lezyon saptandı. Laparoskopik kolesistektomi uygulanan hastada patolojik incelemede lenfovasküler veya perinöral invazyon göstermeyen iyi farklılaşmış adenokarsinom saptandı. Takipte herhangi bir komplikasyon görülmedi. Bu olgu sunumunda, genç yaş grubunda en yaygın etiyolojileri dışladıktan sonra safra kesesi kanserini ayırıcı tanı olarak düşünmenin önemini vurguluyoruz.

Anahtar Kelimeler: Safra kesesi kanseri, kanser, genç yaş

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INTRODUCTION

The gallbladder is a pear-shaped intra-abdominal cavity small organ located in the right upper quadrant (RUQ) on the undersurface of the liver and functions as a condensing storage house of bile before its release into the small intestine (1). Similar to any other organ in the body, the gallbladder may undergo malignant changes, and hence, cancer develops. Gallbladder cancer was first described in 1777 by Maxmillan de Stol (2).

Gallbladder cancer (GBC) is a relatively unusual illness with variable incidence globally. According to global cancer statistics in 2018, approximately 219,420 new cases were recorded worldwide, representing a percentage of 1.2% of all other cancer sites (3, 4). According to GLOBOCAN 2018 data, gallbladder cancer is considered the 22nd most incident type of cancer however, it is the sixth most prevalent cancer of the gastrointestinal tract and the most common cancer of the biliary tract (1, 5). The highest frequency of the disease is found among females over the age of 65 years (2).

GBC can be discovered incidentally, such as during laparotomy or histological examination. However, GBC can be clinically obvious and show evidence of local invasion, large-scale regional nodal metastasis, encasement of blood vessels, and distant metastases (6).

Generally, GBC is considered an aggressive disease among malignancies of the biliary cancers with a short median survival period (6). In that the prognosis is poor, only about a 32% five-year survival rate for lesions confined to the gallbladder mucosa and a 10% one-year survival rate for more advanced stages. In addition, in autopsy studies throughout the world, gallbladder cancer represents 80% to 95% of cancers of the biliary tree (2).

There are marked regional and ethnic variations in the incidence of gallbladder cancer. The highest mortality rates have been reported in India and Hispanics. Incidence rates are much lower in Europe and India (2).

In addition, there is a clear association between chronic cholelithiasis and gallbladder cancer worldwide. Aside from gallstones and female sex, some associated risk factors were discovered to favour the establishment of gallbladder cancer as neoplastic initiators. Unknown internal and probiotic mutagens and neoplastic promoters; including chronic inflammation and infection, were observed to contribute to the development of GB adenocarcinoma (2). For example, gallbladder cancer has been found to be linked to chronic infection with *Helicobacter bilis* and *Salmonella typhi* (7).

Surgery is the most efficient and possible curative management. Proper resection is considered to be curative for early-stage neoplasms; nevertheless, surgical intervention is not effective in many patients, as they have advanced disease due to late presentation (6). Unfortunately, patients who are found to be beyond surgical resection or have distant metastases have a poor prognosis. Open surgical resection is recommended for patients with suspected GBC. Efficient therapeutic choices for managing advanced gallbladder cancer are emerging, including adjuvant combination chemotherapy and targeted therapy. In cases of advanced disease, palliation is the mainstay of management, and endoscopic metallic stents for biliary obstruction are used to improve the quality of life (6). In this case report, we present a case of gallbladder adenocarcinoma in a 17-year-old patient.

CASE PRESENTATION

17 year old male with average weight patient who was previously healthy presented to the emergency room complaining of abdominal pain for several hours prior to presentation. The pain was vague and generalised with no other symptoms, such as vomiting, anorexia, and nausea. There were no constitutional symptoms such as headache, fever, or weight loss. There was no history of any medical diseases, such as haemolytic anaemia.

Moreover, the clinical examination showed no localised tenderness, negative Murphy's sign, rigidity, or guarding. Initial workup showed leukocytosis and mild elevation in liver enzymes, otherwise normal CBC and Biochemistry results (Hb: 14 g/dl WBC: 16.9 10^3/µL PLT:399 10^3/µL, AST: 59 U/L, ALT: 75 U/L, Total Bilirubin: 5.9 µmol/L, Creatinine: 41 µmol/L, Albumin: 42 g/L, Potassium: 4.7 mmol/L and Sodium: 139 mmol/L) and x-ray imaging did not reveal any acute surgical condition. A primary ultrasound of the abdomen and pelvis imaging was performed, showing no gallbladder stones, pericholecystic oedema with normal wall thickening. In addition, there was no hydronephrosis or free fluid collection.

The decision to admit this patient to our hospital for further evaluation was made. Thorough history shows no similar attacks of abdominal pain, changes in bowel habits, dyspepsia, or changes in the colour of urine or stool. There was also no evidence of a family history of malignant diseases, particularly gallbladder or liver cancers. Another confirmatory ultrasonography study was conducted in the presence of an intraluminal hyperechoic irregular margin lesion attached to the wall of the gallbladder fundus without colour flow. The liver was homogenous, measuring approximately 14.5 cm craniocaudally at the midclavicular line with no obvious focal lesions. The spleen was normal in size and shape with no focal lesions. Both kidneys were normal in size, position, and corticomedullary differentiation.

Subsequently, the patient was scheduled for a surgical intervention. Intraoperative laparoscopy revealed a

nodule-like lesion adjacent to the gallbladder fundus and an intraoperative gross image of the fatty liver. Moreover, a histopathological study demonstrated the presence of a gallbladder biliary-type well-differentiated adenocarcinoma measuring 2.5 cm in the greatest dimension, with no definite lymphovascular perineural invasion. In addition, the cystic duct margin was free of tumour invasion (Figure 1).

The pathological results of a true cut biopsy of the liver showed a disturbed architecture with a vague nodular pattern and septal fibrosis, with an overall picture suggesting hepatitis. The patient's postoperative recovery was uneventful. The patient was discharged. Unfortunately, the patient was lost to follow-up as he travelled to another city.

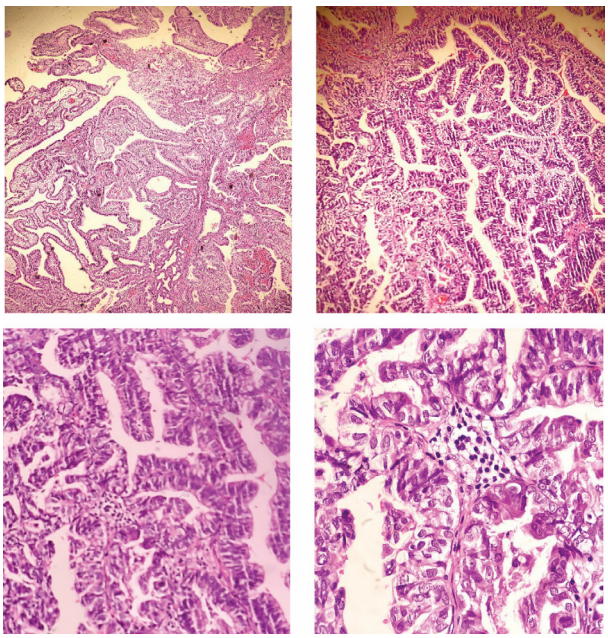

Figure 1: A well-differentiated adenocarcinoma of the gallbladder, biliary type, and 2.5 cm in the greatest dimension. Histological staging is pT2a Nx Mx

DISCUSSION

GBC is an uncommon malignancy that affects the elderly in the first place (1). Studies validate a percentage of 0.26% cumulative risk of gallbladder cancer for females and 0.25% for males up to 74 years of age (5).

Gallbladder malignancy is the most common primary cancer of the biliary tract. Adenocarcinomas arising from secretory cells are nearly the typical form of GB malignancies. Papillary adenocarcinoma is a common form of gallbladder adenocarcinoma that materialises from papillary cells and assists in promoting bile motility in the gallbladder.

It is worth mentioning that the incidence of GBC differs geographically. For example, the United States of America (USA) has a lower incidence than the rest of the world, and Eastern Europe, East Asia, and Latin America denote the highest incidence rates (5).

Gallbladder cancer presents a higher proportion of malignancy mortality than incidence. To clarify, GBC mortality accounts for 1.7% of all cancer-related deaths, although its incidence accounts for only 1.2% of all cancer diagnoses (5). This is due to the poor prognosis of gallbladder cancer, which is attributed to its late diagnosis. For instance, recent epidemiological studies in the USA have revealed that 43% of gallbladder cancers are diagnosed after metastasis to neighbouring structures. However, only 42% of cases were identified after spreading to lymph nodes or distant organs (5).

A retrospective study performed in Jordan between 2002 and 2016 revealed that the GBC rate and histological patterns among patients who underwent cholecystectomy in the northern region were 0.003. Adenocarcinoma remained the dominant type, accounting for 87% of the cases (8). Out of all targeted population, those who underwent cholecystectomies at the time of the study, only 31/11,391 (0.27%) patients had GBC confirmed by histopathology with a mean age of 68 (8). Similarly, in another study carried out in Qatar, five cases per year were diagnosed with GBC with a total of 35 cases in years, which represent the study period. In other words, GBC has an annual incidence of 0.2/100,000 people in Qatar. The median age of the patients was 54 years (3).

Malignancy of the gallbladder is tremendously rare in the young age group and children, with only two case reports available in the English literature and few in the non-English literature (7). However, a 15-year-old boy with gallbladder carcinoma was reported in a study by Muduly et al. (3). Similarly, this report presents a case of GBC in a 17-year-old boy.

Similar to all malignancies, several risk factors predispose patients to cancerous neoplastic growth. In addition to gallstones, age, genetics, obesity, chronic infection and occupational exposure to mutagens are some vital aetiological factors for harbouring gallbladder cancer (5).

Chronic inflammation often leads to gallbladder adenocarcinomas. Physiological cell signalling and cell growth are disrupted. Additionally, gallbladder cancer may be preceded by cholelithiasis in approximately 20 years. Approximately 85% of the patients with cholelithiasis develop GBC. This is assumed to be due to the chronic irritation caused by gallstones, along with the carcinogen production, i.e secondary bile acids. Consequently, sequential growth of metaplasia, hyperplasia, dysplasia, and then carcinoma may occur. Although gallstones are

ultimately linked to the aetiology of gallbladder cancer, their role remains unclear (5).

Calcification of the gallbladder is termed as a porcelain gallbladder attributed to its morphology on radiographic studies. Porcelain GB is particularly commonly observed among middle-aged females or those who are overweight. Through scientific history, porcelain gallbladder has been linked to gallbladder malignancy, with an incidence rate above 60%; however, recent studies have demonstrated a less than 6% accompanying incidence (5).

Potential cancerous growth has been observed in gallbladder polyps for several decades. The exact pathogenesis of this malignancy is still not well understood. In the literature, 23% of the polyps demonstrated malignant changes during the follow-up period. Polyps that have a length of more than 1 cm are noted to be more prone to malignancy. Currently, there are no strict guidelines regarding the follow-up schedule for small asymptomatic polyps, although some studies have concluded that polyps less than 10 mm in length have the capacity to become cancerous (5). In this case report, there were no previous predisposing factors for gallstones, and abdominal ultrasound imaging revealed that the patient had a gallbladder polyp, rather than a stone.

Genetic studies have implied that multiple genetic mutations are involved in gallbladder cancer. Most are tumour suppressor genes or common oncogenes such as c-*erb-B2, KRAS*, *P16*, and *TP53*, which are also implicated in other types of cancers. Thus, they cannot be uniquely hypothesised to be driving mutations in GBC (5). In addition, diabetes is also a risk factor for GBC. Controlling diabetes and high-density lipoprotein levels may reduce GBC levels. Similarly, obesity and being overweight are associated with a risk of GBC (6). In this case, the patient had an average weight and no previous medical diseases, such as diabetes mellitus. Also, unfortunately, genetic study is not available at our facility.

The clinical presentation is not explicit and may include abdominal pain, loss of weight, pyrexia, and jaundice, which are often observed in acute cholecystitis and other non-malignant gallbladder diseases along with some other abdominal malignancies (6). Moreover, most GBCs are still incidentally diagnosed in patients having cholecystectomy for gallstones or gallbladder polyps (8).

Furthermore, in the study carried out in Jordan, almost 70% of patients were diagnosed by chance, whereas in the study conducted by Sulieman et al. in Qatar, the intraoperative suspicion of the presence of the gallbladder was observed in 8.6% of the studied population and proven by intraoperative frozen section (3, 8). In this same study, of all GBC diagnosed cases, 40% were discovered by chance, and another 40% were confirmed by histopathology prior to surgery; in that, tissue core needle biopsy and cytological study by fine needle aspiration were conducted (3). This corresponds to what we found in our case study; in that, our patient was incidentally diagnosed with GB adenocarcinoma after laparoscopic cholecystectomy due to a GB polyp.

Therefore, it is crucial to make a diagnosis in an early setting. Ultrasonography, computed tomographic scan (CT), and magnetic resonance imaging (MRI) have improved the ability to differentiate and select the proper management. In addition, endoscopic ultrasound (EUS) has acceptable sensitivity and can differentiate non-malignant gallbladder conditions from frank gallbladder cancer (6). At initial detection, in 40-65% a mass-occupying lesion was identified in patients with GBC. A large, GB lumen filling or replacing mass with evident direct invasion of the surrounding parenchymal tissue of the liver is strongly suggestive of GBC (6). Interestingly, in the study by Sulieman et al., late presentation was observed in 11.4% of patients as they had metastatic disease on imaging (3).

In imaging, GB cancerous neoplasms may present as focal or diffused asymmetrical wall thickening. Nevertheless, these features can be related to variable benign differential diagnosis, such as acute and chronic cholecystitis, xanthogranulomatous cholecystitis, and adenomyomatosis. Moreover, diffuse hepatic or systemic diseases, such as acute hepatitis, portal hypertension, and congestive heart failure can have similar presentation and findings (6). In our case, ultrasonography showed an intraluminal hyperechoic irregular margin lesion attached to the wall of the gallbladder fundus, without colour flow.

Surgery was the only treatment option available. A small group of patients of patients are diagnosed with the initial clinical phase and can be completely cured by cholecystectomy (5, 6). Tragically, cholecystectomy alone is not curative in all stages of the disease, and a more inclusive surgical approach, consisting of gallbladder, liver, and regional lymph node resection, may be needed. Many hepatobiliary surgeons are convinced that an aggressive surgical strategy enhances the survival rate for stage II and III patients. Some scientists recommend gallbladder and adjacent liver resection including or excluding the extrahepatic bile ducts plus regional lymph nodal clearance as the most acceptable surgical approach for selected patients with GBC (6).

In the management of our patient, laparoscopic cholecystectomy was performed using intraoperative findings demonstrating a nodule-like lesion adjacent to the gallbladder fundus along with a gross picture of a fatty liver.

In terms of GBC pathological characteristics, more than 90% of gallbladder cancers a well to moderately differentiated adenocarcinomas. However, some of these are

papillary lesions that arise mainly in the gallbladder lumen. Nevin's and TNM systems are two clinical and/or pathological systems developed to determine the prognosis of gallbladder carcinoma (2).

In 1976, a new staging system was introduced by Nevin et al., in which Stage I Cancer is confined to the mucosa, in Stage II to the muscular layer, and in Stage III to the perimuscular layer. Stage IV demonstrates lymph node metastases, whereas Stage V shows hepatic or other distant metastases (2). Likewise, in the TNM classification, there are five different pathologically identified stages. Stage I tumours are limited to the mucosa or muscular layers, whereas stage II neoplasms invade the perimuscular tissue. The third stage invasion to liver than two centimetres, or regional (hepatoduodenal ligament) lymph node metastasis. Stage IV shows liver invasion greater than two centimetres (Stage IVA) or metastasis to non-regional lymph nodes and/or distant organs (Stage IVB) (2). In this case report, histopathological examination showed a well-differentiated gallbladder adenocarcinoma measuring 2.5 cm with no definite lymphovascular or perineural invasion, which is consistent with early-stage disease.

There is an argument in the literature regarding prophylactic cholecystectomy. Some studies have argued that prophylactic cholecystectomy is recommended in high-risk populations. This conclusion was based on the hypothesis that there is a strong association between long-standing gallstone disease and the development of GBC (6, 8). Nevertheless, cancer is found only in less than 1% of gallbladders resected for common reasons, such as stones or polyps; thus, there is insufficient evidence supporting the indication of prophylactic cholecystectomy for asymptomatic gallstone disease to prevent GBC (6, 8).

In conclusion, this case report highlights a rare instance of gallbladder cancer in a 17-year-old male, emphasising the need for a comprehensive diagnostic workup to aid early detection and consequently treatment. Despite the typical association of GBC with older age and certain risk factors, this case demonstrates that it can occur in previously healthy young individuals without significant predisposing conditions. Further research is warranted to explore the genetic and environmental factors that contribute to early-onset gallbladder cancer.

Informed Consent: Written consent was taken from the parents of the patient for publishing this case report.

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