Gynecomastia in a Filipino Adolescent Male: A Rare Forewarning Sign of Fibrolamellar Hepatocellular Carcinoma

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ABSTRACT

We present a 15-year-old male with a two-year history of gynecomastia and a four-month history of gradually enlarging abdomen and right flank pain. Examination revealed severe stunting with breast mass Tanner Stage 3, penile stage 2, and hepatosplenomegaly. Laboratory investigations showed normal blood counts, liver function tests, alpha-fetoprotein, and beta-human chorionic gonadotropin. The imaging findings demonstrated multiple confluent masses in the liver, histologically diagnosed as fibrolamellar hepatocellular carcinoma.

Keywords: gynecomastia, fibrolamellar hepatocellular carcinoma, hepatic calcification

INTRODUCTION

Primary liver neoplasms are extremely rare in the pediatric age group, comprising 0.3% to 2% of all pediatric tumors. Liver tumors may either be benign or malignant.[1] The benign tumors include hamartoma, hemangioma, adenoma, and focal nodular hyperplasia, while the malignant ones are hepatoblastoma, hepatocellular carcinoma, and rhabdomyosarcoma.

In children, hepatoblastoma and hepatocellular carcinoma are equally common in the Western world. Still, hepatocellular carcinoma is more common in some regions of Africa and East Asian countries due to the higher prevalence rate of hepatitis B and C infection. There are two variants of hepatocellular carcinoma. The classic type presents early in life with multifocal lesions and is associated in 20-25% of cases with cirrhosis secondary to underlying liver disease. On the other hand, the fibrolamellar type is seen in older children and adolescents, usually solitary, and is diagnosed in those with no or minimal liver disease.[2]

There are limited reports of fibrolamellar hepatocellular carcinoma (FLC HCC) in the pediatric age group. A review of literature from 1980 to 2020 showed that there are presently only 103 children reported with ages ranging from 7 months to 18 years of age. Among these, only three cases presented with gynecomastia. Of the 102 cases, 78 (76%) were diagnosed after resection and 24 (24%) by liver biopsy. Ninety-six are alive and well after resection and chemotherapy, while the rest succumbed to end-stage liver disease two years after diagnosis.[3-9] In 2019, the Division of Pediatric Hematology-Oncology of the Cincinnati

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Children's Medical Center reported 32 patients with hepatocellular carcinoma, seven of whom had a fibrolamellar type. The initial presentation of these seven patients was not discussed. Of the seven, only two are alive.[10]

A review of the Philippine Pediatric Society Disease registry in the last 15 years (2006 up to April 2021) showed 189 cases of hepatocellular carcinoma out of 4,734,485 registry entries. However, patients were not classified as to whether they were the classic or fibrolamellar variant. Presently, there is no local report of fibrolamellar carcinoma, whether in adults or children. Local accounts are limited to adults with hepatocellular carcinoma.[11]

The authors present an adolescent male with a history of gynecomastia but sought consult for abdominal enlargement. He was eventually diagnosed with fibrolamellar hepatocellular carcinoma. Both parents were informed and gave verbal consent for the case to be reported. Consent was also obtained from the patient.

CASE REPORT

A 15-year-old boy presented with a two-year history of an enlarged breast which was considered normal by a local physician. He remained asymptomatic until four months before his consult when he developed dizziness, right flank pain, and a progressively enlarging abdomen. An abdominal ultrasound was done, which showed multiple confluent hepatic masses on both liver lobes, and the boy was eventually referred to our institution. There was no weight loss, urinary or bowel changes, and the child continued to have a good appetite. He could attend school and was a competitive tennis player until the time of his consult. There is no history of cancer in the family.

On physical examination, the patient was severely stunted (weight: 31.50 kg; body mass index: <-2; height: 142 cm; height for age: <-3) with a non-tender breast tissue palpable and elevated as a small mound with enlargement of the areola and no discharges, classified as Tanner Stage 3. The abdomen was distended with visible veins. The liver was hard, measuring eight centimeters from the right costal area and eight centimeters subxiphoid. The spleen measured five centimeters below the left costal margin. The heart and lung findings were unremarkable. There were no clubbing, palmar erythema, or spider angiomas. There was scant penile and axillary hair with a penile length of 3 to 4 cm, classified as Tanner stage 2.

Laboratory investigations showed normal blood counts, prothrombin time, transaminases, and serum albumin. Alpha-fetoprotein and beta-human chorionic gonadotropin levels were acceptable. Viral screening for hepatitis B and C was both non-reactive. Radiographs showed unremarkable chest findings and a bone age consistent with a chronologic age of 15 years. An abdominal computed tomography scan revealed a markedly enlarged liver with innumerable confluent hypodense masses in both lobes. The lesions on the left lobe had a more prominent arterial vascular supply with the presence of calcifications. Minimal ascites were noted at the perihepatic, right, and left paracolic and pelvic spaces (Figure 1). Hepatocellular carcinoma was considered, and the patient eventually underwent an ultrasound-guided liver biopsy.

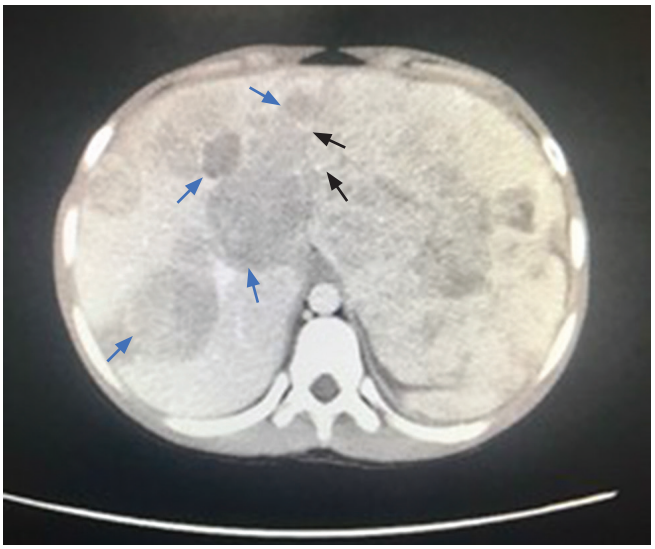

Figure 1. Computer Tomography of the patient's liver showing multiple confluent hypodense nodules *(blue arrows)* with calcifications *(black arrows)* at the left lobe.

Histopathology revealed nests of large polygonal-shaped tumor cells with abundant granular eosinophilic cytoplasm surrounded by collagenous stroma suggestive of FLC HCC (Figure 2). The non-neoplastic liver parenchyma is notable for zonal fatty changes (Figure 3).

On follow-up one week after a biopsy, the patient developed sudden left-sided weakness and was diagnosed with a thrombotic ischemic stroke secondary to tumor emboli. Ischemic infarcts along the cortical and subcortical aspect of the right frontoparietotemporal lobes were noted on CT scans of the brain. Supportive treatment was instituted, and he recovered 80% of his motor function. Due to this incident, the family decided that no further treatment would be given for the patient's liver tumor. The boy is alive three years after his diagnosis.

DISCUSSION

We present a 15-year-old Filipino boy diagnosed with fibrolamellar hepatocellular carcinoma (FLC HCC), an extremely rare disease that occurs at a rate of only 0.2 per 100,000 population. He also had an unusual presentation of a two-year history of gynecomastia.

Most of the patients with FLC HCC usually present with the triad of a palpable right upper quadrant mass, abdominal pain, and weight loss.[8,12] In a report of 35 cases from 1995, 25 (71%) consulted for abdominal pain.[13] However, some

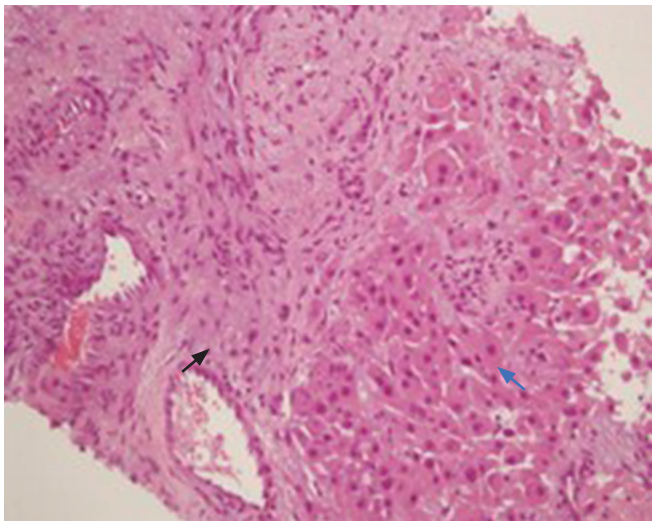

Figure 2. Large polygonal cells *(blue arrow)* with large nuclei and eosinophilic cytoplasm separated by lamellar bands of fibrous stroma *(black arrow)* (H&E, 40x).

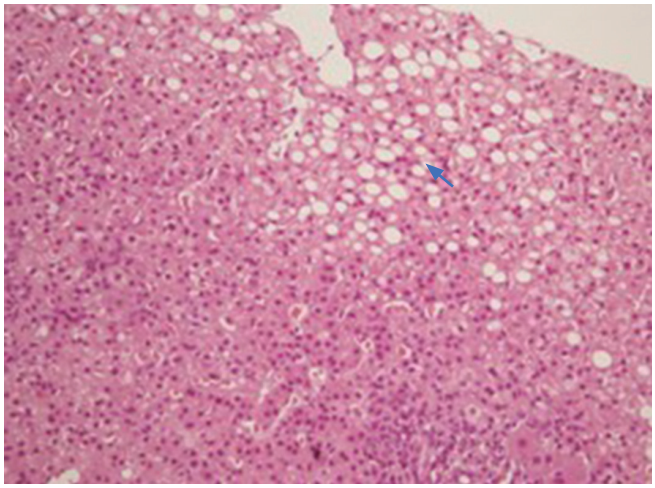

Figure 3. Fatty changes seen in fibrolamellar hepatocellular carcinoma *(blue arrow)* (H&E, 40x).

patients may have atypical presentations such as thrombotic endocarditis, obstructive jaundice, and bone metastasis.[14-16]

A 16-year-old female was described to present with thrombophlebitis of the leg.[4] Gynecomastia, as a presenting symptom, similar to our patient, has been reported in only three patients with the disease, ages 11, 13, and 17 years old.[5,6,16] Gynecomastia may be benign and physiologic in adolescent boys. It usually peaks at ages 13 to 14 years, but should resolve within six months up to two years after onset.[17,18] This could be why our patient's gynecomastia was initially diagnosed as normal when he was 13 years old.

There is no specific recommendation on whether endocrinologic investigations are needed in pubertal gynecomastia. Since the condition occurs due to an imbalance of the estrogen-testosterone hormones, some physicians recommend that levels of estradiol, testosterone, human chorionic gonadotropin, and luteinizing hormone are warranted if the breast mass is rapidly increasing, > 4 cm in size and there is presence of symptoms including tenderness and discharge, which our patient did not have.[19] At the time of consult in our institution, the hormone levels were no longer tested. We surmised that the gynecomastia, associated with severe stunting and delayed puberty, was related to the liver mass. This phenomenon is attributed to the increased aromatization of adrenal androgens, dehydroepiandrosterone sulfate, and dehydroepiandrosterone to estrone and estradiol circulating in the liver.[5,20]

In the presence of a palpable hepatic mass, a diagnostic ultrasound-guided puncture was done on our patient, which confirmed the diagnosis of FLC HCC on histology.[21] Findings of our patient suggestive of fibrolamellar over classic hepatocellular carcinoma include a prolonged history of two years from the onset of gynecomastia without constitutional symptoms of weight loss and anorexia, the absence of underlying liver disease, a nonreactive HBsAg, indicating an absence of hepatitis B infection and a normal level of alpha-fetoprotein. The classic hepatocellular carcinoma in children is usually secondary to a hepatitis B infection acquired during infancy with elevated alpha-fetoprotein. In our patient, we did not see the characteristic CT scan finding in FLC HCC of a well-defined large tumor with lobulated margins and a central scar with fibrous septa.[16] Features, however, on our patient's imaging included the presence of calcification and hyper attenuation during the hepatic arterial phase, which was observed in 30-65% and 80% (25 of 31 patients), respectively, of FLC HCC cases. The presence of lymphadenopathy, suggesting metastases, was not observed in our patient, although the CT scan was done one month before the thromboembolic stroke, suggesting microvascular invasion. There are no reports of thromboembolic stroke associated with FLC HCC, but there is an account of a 26-year-old Caucasian man who developed a cerebellar stroke associated with sorafenib treatment for FLC HCC.[22]

The patient's family opted for no further treatment for the case and are aware of the guarded prognosis. Liver resection is the treatment of choice since most FLC HCC patients are young and have non-cirrhotic livers with low comorbidities. In 206 patients diagnosed with FLC HCC aged 1 to 62 years old, 44% underwent partial hepatectomy; 17% had liver transplantation; 10% were given chemotherapy, and 29% had no specific treatment reported. In post hepatectomy patients, the one-year and five-year survival was 93% and 70% compared to 86% and 34% in post-transplant patients.[23] Recurrence occurred 10 to 30 months after resection with rates ranging from 36% to 100%.[23] Certain factors that predispose the patient to recurrence include the presence of metastasis, lymphadenopathy, and macrovascular invasion.[12, 23]

CONCLUSION

In conclusion, we reported a 15-year-old boy who presented with a two-year history of gynecomastia followed by a recent onset of a rapidly growing abdomen. Biochemical, imaging and histological work-ups revealed that he had fibrolamellar hepatocellular carcinoma, a rare type of primary liver tumor that affects mainly adolescents. The disease should be considered when presented with an adolescent male with gynecomastia, as early diagnosis would result in prompt treatment.

Statement of Authorship

Both authors participated in the data collection and analysis and approved the final version submitted.

Author Disclosure

Both authors declared no conflicts of interest.

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REFERENCES

1. Meyers R. Tumors of the Liver in Children. Surg Oncol. 2007; 16: 195-203.
2. Zheng H, Finn L, Murray K. Chapter 48. Neoplasms of the Liver. In Wyllie R, Hyams J, Kay M, Pediatric Gastrointestinal and Liver Disease, Philadelphia. Elsevier. 5th Edition. 2016. 582-588.
3. Darcy D, Malek M, Kobos M. Prognostic Factors in Fibrolamellar Hepatocellular Carcinoma in Young People. J Pediatr Surg. 2015; 50: 153-156.
4. Mansouri D, Nhieu J. Fibrolamellar Hepatocellular Carcinoma: A Case Report with Cytological Features in a Sixteen-year-old Girl. Diagn Cytopath., 2011; 34: 568-71.
5. McCloskey J, Germain-Lee E. Gynecomastia as Presenting Sign of Fibrolamellar Carcinoma of the Liver. Pediatrics. 1988; 82(3): 379-82.
6. Agarwal V, Takayama K, Van Wyk J. Molecular Basis of Severe Gynecomastia associated with Aromatase Expression in a Fibrolamellar Carcinoma. J Clin Endocrinol Metab. 1998, May; 83(5): 1797-1800.
7. Craig J, Peters R. Fibrolamellar Carcinoma of the Liver: A Tumor of Adolescents and Young Adults with Distinctive Clinicopathologic Features. Cancer. 1980; 46(2): 372-9.
8. Matsuda M, Anemiya H. Typical Fibrolamellar Hepatocellular Carcinoma in a Japanese Boy: A Report of a Case. Surg Today. 2013: 44; 1359-66.
9. Katzenstein H, Krailo M. Fibrolamellar Hepatocellular Carcinoma in Children and Adolescents. Cancer. 2003; 97(8): 2006-11.
10. D'Souza AM, Towbin AJ, Clinical Heterogeneity of Pediatric Hepatocellular Carcinoma. Pediatr Blood Cancer. 2020 Jun;67(6): e28307.
11. Daez M, Ong J, Lombiy A, Libuit J, Vicente I, Firmalino G, Carpio G. Demographic Profile and Treatment Outcomes of Filipino Patients with Hepatocellular Carcinoma in a Liver Tumor Registry. Acta Med Philipp.2014;48.
12. Rendon L, Garcia V, Cadavid J. Case Report of a Fibrolamellar Hepatocarcinoma, A Rare Tumor of Young Adults. Rev Col Gastroenterol. 2014; 29(4): 423-8.
13. Saab S, Yao F. Fibrolamellar Hepatocellular Carcinoma: Case Reports and a Review of Literature. Dig Dis Sci. 1996; 41(10): 1981-1985.
14. Torbenson M. Fibrolamellar Carcinoma: 2012 Update. Scientifica. 2012: 1-15.
15. Soyer P, Roche A, Levesque M. Fibrolamellar Hepatocellular Carcinoma Presenting with Obstructive Jaundice: A Report of Two Cases. Eur J Radiol. 1991; 13(3):196-8.
16. Katsumi M, Taguchi S, Taguchi T, High Aromatase Activity and Overexpression of Epidermal Growth Factor Receptor in Fibrolamellar Hepatocellular Carcinoma in a Child. J Pediatr Hematol Oncol. 2011; 33(5): 195–7.
17. Lemaine V, Cayci C, Simmons P. Gynecomastia in Adolescent Males. Semin Plast Surg. 2013; 27(1); 56-61.
18. Dickenson G. Gynecomastia. Am Fam Physician. 2012; 85(17): 716-22.
19. Braunstein GD. Clinical Practice. Gynecomastia. N Engl J Med. 2007 Sep 20;357(12):1229-37.
20. Muramori K, Taguchi S, Taguchi T, Kohashi K, Furuya K, Tokuda K, Ishii E. High Aromatase Activity and Overexpression of Epidermal Growth Factor Receptor in Fibrolamellar Hepatocellular Carcinoma in a Child. J Pediatr Hematol Oncol. 2011 Jul;33(5):e195-7.
21. Estrella Díez E, Álvarez Higueras FJ. Fibrolamellar Hepatocellular Carcinoma: A Rare Entity Diagnosed by Abdominal Ultrasound. Rev Esp Enferm Dig. 2016 Aug;108(8):494-5.
22. Vandewynckel YP, Geerts A, Verhelst X, Van Vlierberghe H. Cerebellar Stroke in a Low Cardiovascular Risk Patient Associated with Sorafenib Treatment for Fibrolamellar Hepatocellular Carcinoma. Clin Case Rep. 2014 Feb;2(1):4-6.
23. Mavros M, Mayo S, Hyder O. A Systematic Review: Treatment and Prognosis of Patients with Fibrolamellar Hepatocellular Carcinoma. J Am Coll Surg. 2012; 215 (6): 820 – 8.