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Crohn's Disease, Hodkin's Lymphoma, and Hepatocellular Cancer: A Case Report

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ABSTRACT

Crohn's disease (CD) is rare in the World and in the Philippines. The occurrence of hepatocellular carcinoma (HCC) in CD is rare. Hodgkin's Lymphoma (HL) in the small intestine is rare.

Here is a 72 year old male nonsmoker nonalcoholic with CD, HCC, ileal HL, diabetes mellitus, and hypertensive arteriosclerotic cardiovascular disease (HASCVD).

Keywords: Crohn's Disease; Hodgkin's Lymphoma; Hepatocellular Cancer; Case Report

INTRODUCTION

The global incidence of Crohn's disease ranges from 23.8 to 29.3 per 100,000 population.[1]

In the Philippines, CD is rare, with an estimated prevalence of 0.35 per 100,000 people and an incidence of 0.07 per 100,000 person-years, according to the Inflammatory Bowel Diseases Club of the Philippines.[2-4]

Patients with CD have an increased risk of developing malignancies, including small bowel, colorectal, and extraintestinal cancers, as well as lymphoma, more commonly Non-Hodgkin Lymphoma (NHL).[5-7] Although non-Hodgkin Lymphoma (NHL) is the more common lymphoid malignancy associated with CD, primary intestinal Hodgkin Lymphoma has been reported, but remains extremely rare. For primary intestinal HL, the ileum is more commonly involved.[8]

Furthermore, HCC in CD patients is exceedingly rare, with only 10 reported cases in literature. To date there have been no known reports of synchronous HCC and HL, making this case an unprecedented clinical occurrence.[9]

CASE REPORT

A 72-year-old, non-smoker, non-alcoholic, male complained of 1 year history of recurrent hematochezia. He was being managed for controlled diabetes mellitus and HASCVD, for which he completed percutaneous coronary intervention three times. Abdominal ultrasound showed gallstones, nephrolithiasis, and renal cyst.

The patient was taking antihypertensive, oral hypoglemic, anticoagulant, and anti-hyperlipidemic medications. Informed consent was obtained from the patient's wife for the use of clinical data and images for educational purposes.

Upon presentation, he underwent gastroscopy showing non-erosive gastritis, gastric polyps, duodenal polyp, and duodenal erosion, with a negative H. pylori rapid urease test. Colonoscopy revealed ileitis with ulcerations, ileocecal valve ulcers with signs of recent bleeding, ascending colon erosions and polyp, internal and external hemorrhoids. A Meckel's diverticulum study was negative. Whole abdomen CT scan showed terminal ileum thickening, fat stranding, and sub-centimeter to enlarged mesenteric lymph nodes.

Two years later, repeat colonoscopy confirmed Crohn's disease (CD), with multiple 5-10 mm ulcers in the terminal ileum and diffuse edematous mucosa from the cecum to the rectum. Histopathology demonstrated chronic inflammation with erosions in the ileum and non-specific chronic inflammation in the ascending colon and rectum, without malignant cells. The patient was not treated with azathioprine.

Two years after his CD diagnosis, the patient presented with abdominal pain and recurrent hematochezia. An F18-DG PET CT scan showed hypermetabolic small bowel segment wall thickening with luminal narrowing, multiple hypermetabolic prominent para-aortic, aortocaval, mesenteric lymph nodes, a hypermetabolic liver mass in segment VIII, hypermetabolic bilateral lung nodules and a non-calcified right upper lobe nodule.

Liver MRI confirmed a segment VIII mass, measuring 3.3 x 4 x 4cm, and an ileal mass with extramural vascular invasion. The patient underwent small bowel segmental resection, and histopathology revealed: poorly differentiated malignancy with prominent necrosis (8 cm tumor extending to mesenteric fatty tissue), and 21 out of 23 lymph nodes positive for tumor involvement. Final histopathologic diagnosis was Classic Hodgkin Lymphoma, Nodular Sclerosis type, with immunohistochemistry of CD20 positive, CD30 positive, and Ki 67% high. EBV was also positive.

A pre-chemotherapy 2D-Echogram showed heart failure with reduced ejection fraction (EF 37%). Despite this, the patient was cleared for chemotherapy and completed six cycles of Adriamycin-Vinblastine-Dacarbazine plus eight cycles of Brentuximab. There was no recurrence of lymphoma after treatment, but with increasing size of the liver mass.

Alpha feto protein (AFP) level was only 1.76 ng/ml, while viral hepatitis markers were negative. There was no evidence of primary sclerosing cholangitis. A core needle biopsy of the segment VIII mass confirmed hepatocellular carcinoma.

Selective Internal Radiation Therapy (SIRT) using Yttrium microspheres with a total dose of 1.0 GBq was performed on the Segment VIII liver tumor. The patient was then started on Lenvatinib, with only 3 months progression-free survival (PFS). Treatment was shifted to atezolizumab with bevacizumab for 6 cycles. Follow-up CT scan showed stable sizes of the liver masses. However, there was development of vertebral bone metastasis with a fracture at C6, resulting in spinal cord compression.

DISCUSSION

Inflammatory bowel disease (IBD), which includes Crohn's Disease (CD) and Ulcerative Colitis (UC), is a relapsing and remitting condition characterized by chronic inflammation at various sites in the gastrointestinal tract, leading to diarrhea and abdominal pain. The inflammation results from a cell-mediated immune response in the gastrointestinal tract. The precise etiology of IBD is unknown, but evidence suggests that normal intestinal flora inappropriately trigger an immune reaction in genetically predisposed patients, possibly involving abnormal epithelial barriers and mucosal immune defense. No specific environmental, dietary, or infectious causes have been identified. The immune reaction involves the release of inflammatory mediators, including cytokines, interleukins, and tumor necrosis factor.[10]

CD is a chronic transmural inflammatory bowel disease that usually affects the distal ileum and colon, with small bowel involvement in 80% of cases. Symptoms commonly include diarrhea and abdominal pain. Hematochezia is rare except in 75-85% of Crohn colitis. Diagnosis is by colonoscopy and imaging studies. Treatment includes 5-aminosalicylic acid, corticosteroids, immunomodulators, anti-cytokines, antibiotics, and often surgery.[10]

Nonpathogenic intestinal bacteria may trigger chronic immune dysregulation in CD.[11,12] It is considered an archetypical barrier disease with disrupted immune maintenance.[13]

CD increases malignancy risk, notably small bowel, colorectal, extraintestinal cancers, and lymphoma.[6] **The relative risk of those cancers compared to the general population is highest for small bowel.[5] Lymphomas associated with CD are predominantly non-Hodgkin lymphoma (NHL), occurring ten times more often than Hodgkin Lymphoma (HL).**[13] Immunosuppressants like TNF blockers and thiopurines contribute to NHL risk.[14]

NHL involves mature B, T, or NK cells and comprises 90% of lymphoma diagnoses. Distinction from HL relies on identifying Reed-Sternberg cells. Whereas 80-88% of HL patients achieve cure with chemotherapy, NHL prognosis varies.[15,16] Classical HL (cHL) is the most common form; Nodular Lymphocyte predominant HL (NLHPL) is less common and shares traits with indolent B-cell NHL.[17]

EBV-positive cHL is more common in males. EBV may also influence IBD-associated lymphomagenesis.[14,18] EBV was detected in 63.6% of CD and 60% of UC. EBV infects B cells, and though most adults are carriers, few develop lymphoma.[19, 20] Our patient was EBV-positive and had nodular sclerosis HL with CD.

Hepatocellular carcinoma (HCC) in CD is rare and its pathogenesis is unclear.[21] HCC may develop due to chronic liver conditions but often appears with primary sclerosing cholangitis, which was absent in this case. The overlap of HL and HCC is extremely rare. The role of EBV in both HL and IBD raises questions of viral-driven malignancy in immune dysregulated settings. While IBD is more clearly linked to HCC in primary biliary cirrhosis, our patient had none.

Treating synchronous hematologic and solid tumors requires prioritization based on cancer biology and aggressiveness. [22] HL, being more aggressive, is usually treated first, with HCC managed based on progression and overall health.

A 2019 report noted four cases of synchronous lymphoma with digestive system carcinoma, including one with both HCC and diffuse large B-cell lymphoma (DLBCL). This patient presented with liver masses on imaging. Hepatolobectomy revealed the synchronous tumors on histopathology. The patient underwent 8 cycles of CHOP, with no evidence of disease at 62 months.[23]

For HL CD30+, Brentuximab plus Doxorubicin, Vinblastine, and Dacarbazine is standard[24], which our patient received.

Intermediate-stage HCC may benefit from SIRT for potential downstaging.[25] Our patient underwent SIRT with stable disease. Unresectable HCC is treated with atezolizumab and bevacizumab.[26] Our patient received this combination but progressed after six cycles.

Malignancies are a leading cause of death in IBD patients. HCC prognosis is poor, with a 5-year survival of 21.6%. Survival drops with disease stage: 37.3% localized, 14.3% regional, 3.5% distant.[27] Metastasis occurs in 30-50% of cases, commonly affecting lungs, lymph nodes, and bones.[28]

CONCLUSION

This case highlights the rarity of synchronous Crohn's disease, Hodgkin lymphoma, and hepatocellular carcinoma in a single patient - a combination not previously reported in literature. It underscores the complex interplay of chronic inflammation, immune dysregulation, and possible viral oncogenesis in malignancy development. Managing multiple primary cancers presents significant diagnostic and therapeutic challenges, requiring careful prioritization of treatment based on disease aggressiveness and patient condition. This case reinforces the importance of a multidisciplinary approach in complex oncologic cases and raises awareness of the potential for rare malignancy associations in patients with inflammatory bowel disease.

DECLARATION

Ethical Approval: Ethical approval was given.

Consent for publication: Informed consent was obtained from the patient's wife for publication of this case report and any accompanying images.

Availability of supporting data: The patient's medical record is available at the hospital for review.

Competing interests: There is no competing interest on behalf of the authors in reporting this case:

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Authors' contributions: Prof Ngelangel wrote the case report. Dr. Ang and Dr. Sandoval-Tan assisted Prof Ngelangel in the writing of the case report and the search for literature relevant to this case. Dr. Habito contributed SIRT literature and the patient response to this.

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Authors' information: Prof Corazon A Ngelangel was the medical oncologist of the patient at Asian Cancer Institute- Asian Hospital and Medical Center (ACI-AHMC), and she is Professor at the University of the Philippines-College of Medicine. Dr Roy Ang and Dr Jennifer Sandoval-Tan are the medical oncology fellow-in-training and consultant, respectively at the University of the Philippines-Philippine General Hospital (UPCMPGH), Department of Internal Medicine Division of Medical Oncology. Dr. Cicero Habito was the Interventional radiologist of the patient at ACI-AHMC.

ABBREVIATIONS

CD: Crohn's disease

HCC: Hepatocellular carcinoma

HL: Hodgkin's Lymphoma

NHL: Non-Hodgkin's Lymphoma (HL

HASCVD: hypertensive arteriosclerotic cardiovascular disease

CT: Computed tomography

F18-DG PET CT: Fluorine-18 fluorodeoxyglucose Positron Emission Tomography computed tomography

MRI: Magnetic Resonance Imaging

CD20: "CD" stands for "Cluster of Differentiation". CD20 is a protein found on the surface of B cells, a type of immune cell. The numbering (20 in this case) signifies the specific protein within the broader "Cluster of Differentiation" designation.

CD30: "CD" stands for "Cluster of Differentiation". CD30 is a protein found on the surface of B cells, a type of immune cell. The numbering (30 in this case) signifies the specific protein within the broader "Cluster of Differentiation" designation.

Ki 67%: "Ki" comes from the city of Kiel, Germany, where the antibody that identifies the protein was first developed. A high Ki-67 index (typically above 30% for breast cancer) suggests a faster growth rate of the cancer and potentially a higher risk of recurrence and spread.

EBV: Epstein Barr Virus

2D-Echogram: 2-dimensional echogram

EF: ejection fraction

AFP: Alpha feto-protein

SIRT: Selective Internal Radiation Therapy

PFS: progression-free survival

C6: Cervical vertebrae #6

IBD: Inflammatory bowel disease

TNF: Tumor necrosis factor

cHL: Classical HL

NLHPL: Nodular Lymphocyte predominant HL

B-cell: Bursa derived cells

T-cell: Thymus derived cells

NK cell: Natural killer cell

CHOP: cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone

SIRT: selective internal radiotherapy

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