journalofclinicalcases.com

Journal of Clinical Cases

ISSN 2769-9366

Case Report

Refractory Septic Shock In Pancytopenia Patient After Azathioprine Induction: A Possible Cause Of Death Of Young Female Crohn Patient: A Case Report.

Dr.Abdu Bedru (Bsc, MD, MPHE)*, Dr.Selamawit Tilahun, MD, Dr.Sisay Gizaw, MD, Dr.Henock Fisseha, MD, Dr.Temare Birhanu,MD.

Dr.Abdu Bedru, Bsc, MD, MPHE, Manager Takaful customer experience hub. Nyala Insurance S.C. Gondar university. Addis Ababa, Ethiopia,
Dr. Selamawit Tilahun MD, Consultant internist and pulmonologist,
Dr.Sisay Gizaw MD, consultant Internist ,neurologist and physiatrist,
Dr. Henock Fisseha MD, consultant Internist , Gastroenterologist ,
Dr. Temare Birhanu MD, Consultant Internist,

Abstract

A 23- year- old female crohn patient was empirically induced with Azathioprine 100mg and prednisolone by mouth. Her complete blood count and liver functions were normal at the treatment initiation. However her condition progressively deteriorates despites taking the drug for a month. Hence she was admitted to medical Intensive Care unit for the diagnosis of Pancytopenia with neutropenic fever and septic shock secondary to possibly Azathioprine toxicity and subsequent sepsis. Azathioprine discontinued and pancytopenia package of management (intravenous antibiotics, vasopressors, and blood products transfusion) initiated. From fifth to ninth day of admission, she was progressively deteriorating despite adding Filgrastim and Hydrocortisone to her prior management. She was diagnosed to have Para spinal myoclonus seizure due to dyseletrolytemia on her 11th day of admission. She was relatively improving and antibiotics discontinued at 16th day of admission. On 18th day of admission, she deteriorated due to fulminant Clostridioides Difficile and or Cytomegalovirus associated Toxic mega colon. On 21st day of admission, her mentation dropped and intubated here after. Moreover Refractory septic shock and Disseminated Tuberculosis were considered. Intravenous antibiotics including antiviral and antifungal reinitiated with Anti Tb drugs at this time. On 25th day of admission, she developed cardiac arrest. Full cycles of CPR done but she could not be salvaged despite the immense efforts. The immediate cause was multi-organ failure secondary to refractory septic shock possibly due Azathioprine and subsequent sepsis induced pancytopenia.

IBD as a disease of western countries now is an obsolete view. Considering the progressive increase in crohn disease, a caring physician must address the multimodal crisis from such disease with vigilance. Azathioprine if given empirically should be in low dose with gradual escalation to prevent subsequent myelosupression (5). This case also revealed the need of early empiric initiation of anti Tb in high risk patient in whom Tb and IBD cannot be differentiated. It is paramount important to consider early surgical intervention in patient with high risk colectomy like ours. More over when a patient develop refractory septic shock with neutropenic fever, it is also wise consider Tuberculosis septic shock and mange accordingly while addressing viral and fungal infection.

INTRODUCTION

Inflammatory bowel diseases (IBD) include ulcerative colitis (UC) and Crohn disease (CD).The prevalence of IBD worldwide exceeded 0.3% (2).Crohn disease though the etiology is unclear is non-infectious chronic intermittent inflammation of the gastrointestinal tract resulted from uncontrolled immune response to a trigger in genetically prone individuals. It causes physical, socio-psychological and economic crisis (3.5, 6, 7).

CD commonly manifest with weight loss, chronic diarrhea, right lower quadrant pain and mass. Thirty percent of patients present with enteropathic arthritis, nail clubbing, uveitis, iritis, episeceleritis, cholithiasis, urolithisis, oral apthus, pyostomatitis vegetans, erythroma nodusum, acrodermatities eteropathica and pyoderma gangrenosum(6,7).

A single gold standard is not available. The diagnosis is confirmed by clinical evaluation and a combination of endoscopic (ulcerations, skip lesions, cobblestone appearance), histological, radiological, and/or biochemical investigations. The differentiation of CD with intestinal tuberculosis is sometimes difficult in the context of Africa. The diagnosis of CD can only be made as a diagnosis of exclusion (5, 6, 7).

Majority of patients present late with severe disease due

***Corresponding Author:** Dr.Abdu Bedru, Bsc, MD, MPHE, Manager Takaful customer experience hub. Nyala Insurance S.C. Gondar university. Addis Ababa, Ethiopia , **Tel :** +251112732675 ,**Email:** abdubedru@gmail.com.
Received: 15-Feb-2025, Manuscript No. JOCC - 4559 **; Editor Assigned:** 28-Feb-2025 **; Reviewed:** 29-Mar-2025, QC No. JOCC - 4559 **; Published:** 31-Mar-2025, **DOI:** 10.52338/jocc.2025.4559
Citation: Dr.Abdu Bedru, Bsc, MD, MPHE. Refractory septic shock in pancytopenia patient after azathioprine induction: a possible cause of death of young female Crohn patient: A case report. Journal of Clinical Cases. 2025 March; 4(1). doi: 10.52338/jocc.2025.4559.

to the fact that the disease had been neglected due to inaccurate diagnosis and inappropriate treatment. IBD is managed by medication and changes in lifestyle.5-ASAs and corticosteroids are highly preferred for the treatment of IBD. Azathioprine or mercaptopurine may be used as an add-on medication to induce remission but is not used as mono therapy. Methotrexate is an alternative to azathioprine. In the West, biological agents (e.g. Infliximab) are the fastest growing segment of the prescription drug market. Around 80% of patients with Crohn disease will eventually have surgery (5, 6, 7, 8).

Diagnosing and managing patient with Crohn disease especially in resource limited setting like Ethiopia is really challenging. The goal of this case report is to shade a light on the clinical presentation of 23-year-old female patient, how the diagnosis made, and the way the patient managed challenges encountered on the standard of care. Moreover it is intended to suggest key clinical recommendation on how to approach high risk crohn disease patient from Tb endemic area when Thiopourine methyltransferase(TMT) testing is not available.

CASE ILLUSTRATION

A 23- year- old female patient was referred from a hospital in Addis Ababa to our St. Paul's hospital with the diagnosis of Right lower quadrant intra-abdominal inflammatory mass secondary to crohn disease for better evaluation and management. Up on presentation to our emergency department, she was complaining worsening of intermittent right lower abdominal cramps and frequent profuse yellowish mucoid diarrhea for the last one week. She has also two-three episodes of vomiting of ingested matter, progressive weight loss, easily fatigability, and poor appetite along with high grade intermittent fever for the same duration which made her unable to walk unsupported even after receiving two bags of blood transfusion at the referring hospital.

She used to have similar illness for the last three years for which she was treated many times with unspecified medications at her nearby clinic but no improvement. A month back, she went to the referring hospital where she was diagnosed to have Crohn disease by abdominal Computerized Tomography (CT) and Colonoscopy. Her abdominal CT showed Ulcerated Ileocaecal valve and localized areas of ulceration in the rectum while her colonscopic biopsy revealed colonic mucosa fragments with cryptitis and mixture of inflammatory infiltrates suggesting chronic active inflammation. There was no granuloma or malignancy.

Accordingly she was initiated Azathioprine 100mg by mouth daily. However her condition deteriorates despite she took the drug for one month. As result she discontinued her medication four day prior to her presentation to our hospital. Moreover her baseline white blood cells (WBC) drops from 4,600/µL(Neutrophil(N)67%,Lyphocyte(L)27.7%) to 740/µL(N13%,L80%), her Hemoglobin (Hgb) from 11.7g/dl(Hematocrit (HCT)35%, Mean Corpuscular Volume (MCV)81.5 fL) to 5.5g/dl and her Platelet (PLT)) from 368,000 /µL to 142,000/ µL. Her C - reactive protein (CRP) and Erythrocyte sedimentation (ESR) were 59 mg/L and 30mm/hr respectively. Otherwise she had no history of previous admission for the same complaints. She had no family history of the same illness or previous tuberculosis. Her HIV status was negative and denied any history of smoking tobacco or drinking alcohol. She was nulliparous with regular menses. She was a bride- to-be. Her stable food was "Injera local bread made of flour of minute seeds of sesame flower plant" with "shiro wot (sauce made of flour of beans mixed with spiced pepper)".

Objectively on arrival, she was critical, emaciated, hypotensive, tachycardeic with feeble but regular pulse, febrile and tachypneic. Her oxygen saturation was 94% at room air. On head to neck examination, the conjunctiva was pale with icteric sclera. There were also yellow crusting nasal vestibular lesions on both nostrils. The abdomen was flat with diffuse direct and rebound tenderness more on the right lower quadrant. There was also palmar pallor. Otherwise the rest physical examinations were unremarkable and she was alert. Her WBC further drops to 420/µL with Absolute Neutrophil Count (ANC) 130/µL, Hgb10.6g/dl, Hematocrit (HCT) 30.4% and Mean Corpuscular Volume (MCV) 80 and PLT=29,000/µL. Serum electrolyte panel showed mild hyponatremia and moderate hypokalemia. Urine analysis showed Leucocyte, +3 protein+3, bilirubin+1, blood+3, urobilinogen+3, WBC3-5, RBC3-7 and many bacteria. The renal function and liver enzymes were normal. Her total bilirubin (BT) and direct bilirubin (BD) were 1.9 and 1.3 respectively.

The second Abdominopelvic CT with contrast showed Long segment distal ileum and multi focal colonic wall thickening (caecum, ascending colon, sigmoid colon and anorectal region with engorgement of vasa recta, mesenteric fat stranding and LAPs secondary to likely active crohn disease. There was also Hepatomegaly with mild fatty liver and Minimal ascites. No abscess or fistula detected.

As per the subjective and objective data discovered, she was diagnosed with Sepsis of GI focus with septic shock, moderate hypokalemia, mild hyponatremia, Crohn with acute flare, Pancytopenia with neutropenic fever secondary to Azathioprine Toxicity and septic DIC. She was initiated intravenous antibiotics (vancomycin, cefepime and metronidazole), KCL and Noreadrenaline. She was also transfused with PLT, Fresh Frozen Plasma (FFP) and Packed Red Blood Cells (PRBCs). She was then transferred to medical Intensive care Unit (MICU) after 48hrs of stay in the emergency and transition ward.

From fifth to ninth day of admission, she started to complain

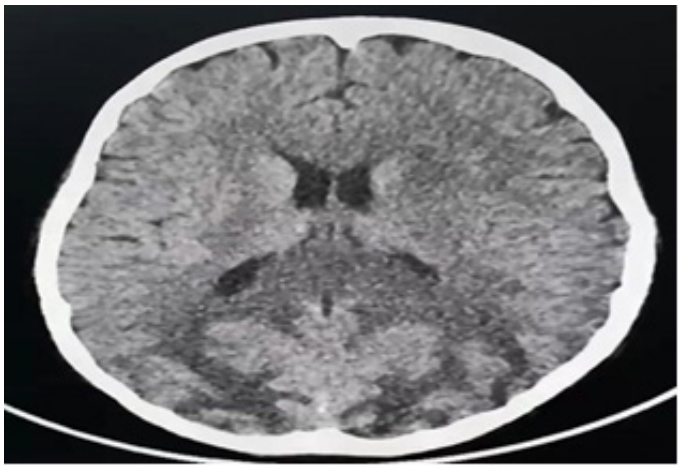
persistent crampy abdominal pain and new onset of intermittent bloody diarrhea which was initially liver like in color and clotted later became profuse tarry stool associated with difficulty of swallowing to solid foods. She was in respiratory distress requiring facemask oxygen support to the level of 10L/minute. Physical examination and Point of Care chest ultrasound (POCUS) revealed fine crepitation with decreased air entry over the lower 2/3 lung fields bilaterally and bilateral pleural effusion with consolidative change. Abdominal examination and POCUS showed positive shifting dullness and minimal ascites. There was vulvar swelling. Moreover she had Grade II bilateral pitting leg edema and diffuse petechial rash over the inner thigh, lower abdomen and upper extremities. Otherwise she was alert and no other pertinent finding identified. Peritoneal fluid analysis showed WBC count 50(N=15%, L=85%), Gene expert not detected, No microorganism seen. Pleural fluid gene expert was also negative for Tuberculosis.

Chest CT showed only bilateral pleural effusion. Vulvar capillary leak syndrome, Severe hypocalcaemia and severe hypomagnesaemia added to her previous problem lists. Subsequently, Folic acid, Cynocobalamin, calcium carbonate, magnesium sulphate, filgrastim, fluconazole, acyclovir, intravenous transexamic acid and hydrocortisone added to her prior management.

On 11th day of admission, she was immensely deteriorating. She started to experience gradual onset of global headache associated with twitching of muscles of neck area initially on the right side later progress to the left side. Otherwise she was alert and no motor deficit detected. Her reflexes both extremities were intact. She had no meningeal signs. Her non contrast brain CT, carotid Doppler, cervical and brain MRI were unremarkable. Para spinal Myoclonus seizure was considered and Sodium valproate added to her management packages.

Figure 1. Chest CT of 23-yr-old female Crohn patient.

Figure 2. Non contrast brain CT of 23-yr-old female Crohn patient.



On 16th day of admission, the patient was feeling healthful and giving her salute to all of us and her mother in particular. The diarrhea and the neck muscle twitching were subsided. She was sub critical. Her Blood Pressure was systolic ranging 125 to 147mmHg and diastolic ranging from 80-102mmHg, Pulse Rate ranging from 64 to 88bpm,Respiratory rate ranging from 20 to 26bpm, her saturation SaO2 ranged from 91-98% 4-6L oxygen support via FM, her temperature 35.8 to 36.9.there was decreased air entry over the posterior 1/3 lung fields bilaterally. S1 and S2 well heard with flat JVP. Abdomen was slightly

distended with direct tenderness in all quadrants. The Vulvar edema subsides. She was alert. On investigation Total WB 1330/µL(N=71.5%),Hgb8gm/dl, and PLT 50,000/µL. The electrolytes were corrected. Hence Sodium valproate, vasopressors, antibiotics were discontinued. There was a hope of recovery and cure by all attending physicians and nurse, families especially by her bride groom-to-be.

On 18th day of admission, she felt severely ill. She started to experience severe headache and blurred vision followed by two episodes of myoclonus seizure of the upper extremity characterized by up rolling of the eyes and impaired consciousness each lasting 30 second with post-ictal confusion. Furthermore her abdominal distension and pain worsened accompanied by failure to pass flatus and stool. She was normotensive but tachycardeic and tachypneic. Her temperature was normal. She maintained her saturation with 5L oxygen support via FM Abdomen was distended with direct tenderness in all quadrants and hypertypanic. Digital examination of the rectum showed clotted blood but no stool. Otherwise she was alert. Abdominal x ray showed complete large bowel obstruction. Fulminant CDI associated Toxic mega colon considered and oral vancomycin initiated. Surgery and colonoscopy deferred.

On 21st day of admission, she was further deteriorating. She had two episodes of profuse melena associated with change in mentation. She was intubated and put on mechanical ventilator. Her GCS was 8T. On investigation, Total WB 2550/µL(N=75%),Hgb8gm/dl, PLT 67,000/µL, PT 17.5, PTT 31.9, and INR 1.45.Refractory septic shock and Disseminated Tuberculosis were considered. Intravenous antibiotics (metronidazole, ciprofloxacillin and meropenum) and Anti Tb drugs initiated.

Figure 3. Melena of 23-yr-old female Crohn patient.

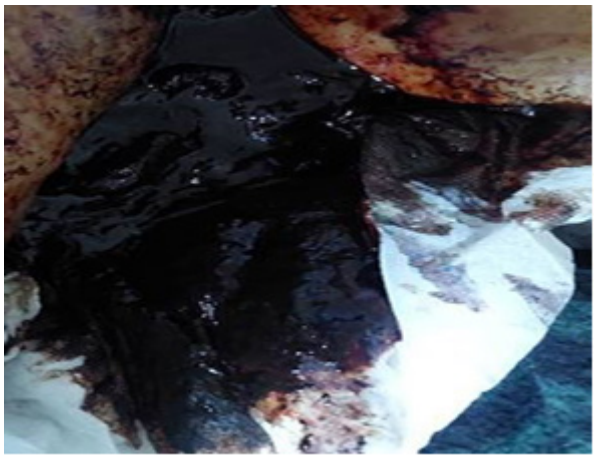
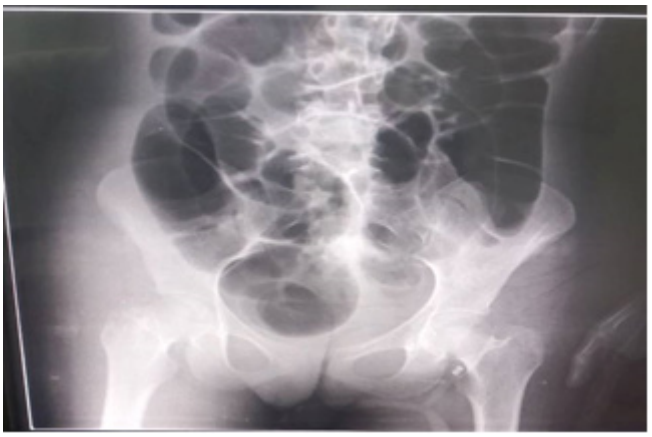


Figure 4. supine abdominal x ray of 23-yr-old female Crohn patient.



On 24th day of admission, she was progressively deteriorating. She was having frequent profuse tarry stools. Her mentation was dropping. Her abdomen was progressively increasing in size. There was blood secretion from the ETT tube. Her blood pressure was recordable. The peripheral pulse was not palpable. Her temperature was 24.30C. The sclera was edematous and icteric. Abdomen was full with hypoactive bowel sounds. There was profuse tarry stool and clotted blood coming out from vagina. She had G IV edema with cold extremities. Her GCS was 2T.The WBC 270/µL (N79.9%,/L16.6%),Hgb 6.6gm/dl, PLT5000/µLand was hypokalemic. Vasopressor escalated and KCL reinitiated.

On 25th day of admission she developed cardiac arrest. Full cycles of CPR done but she passed away. The immediate cause is multi-organ failure secondary to refractory septic shock with DIC.

Figure 5. Pattern of white blood cells and absolute neutrophil count in young female crohn patient.

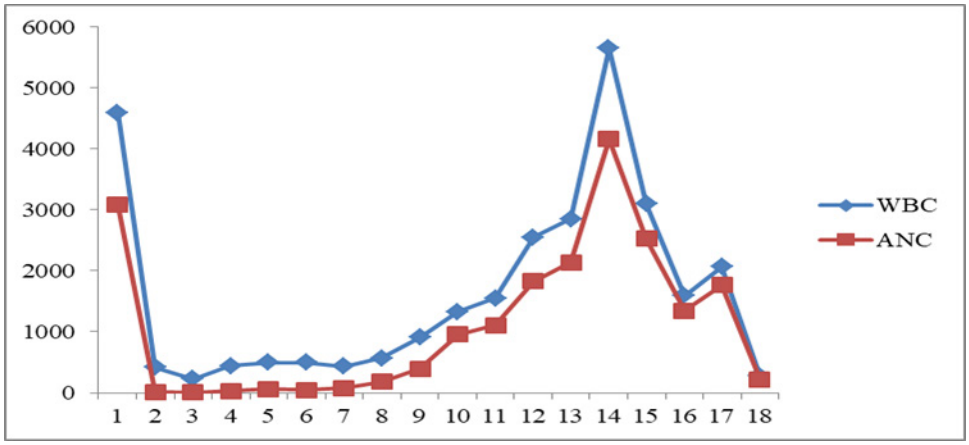


Figure 6. Pattern of Hemoglobin in young female crohn patient.

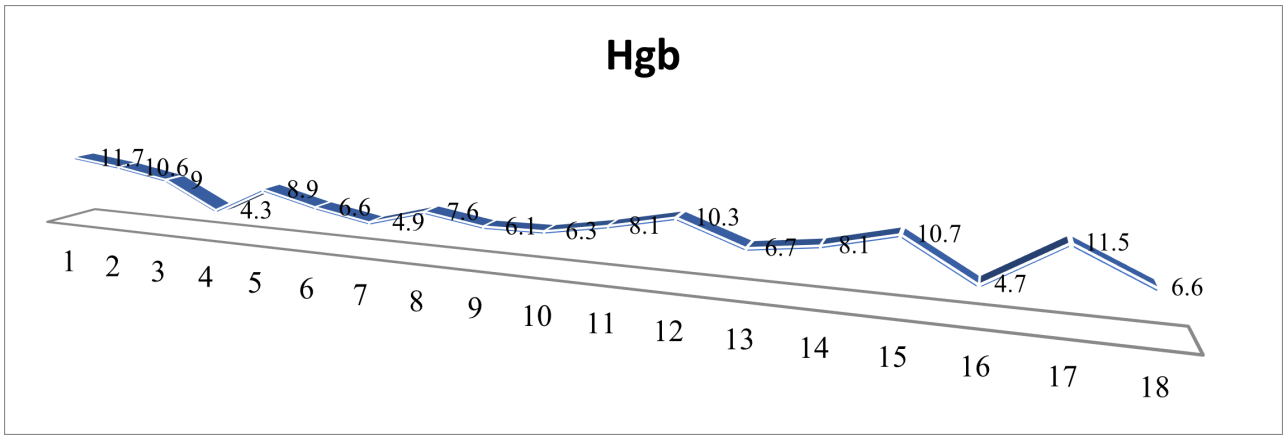
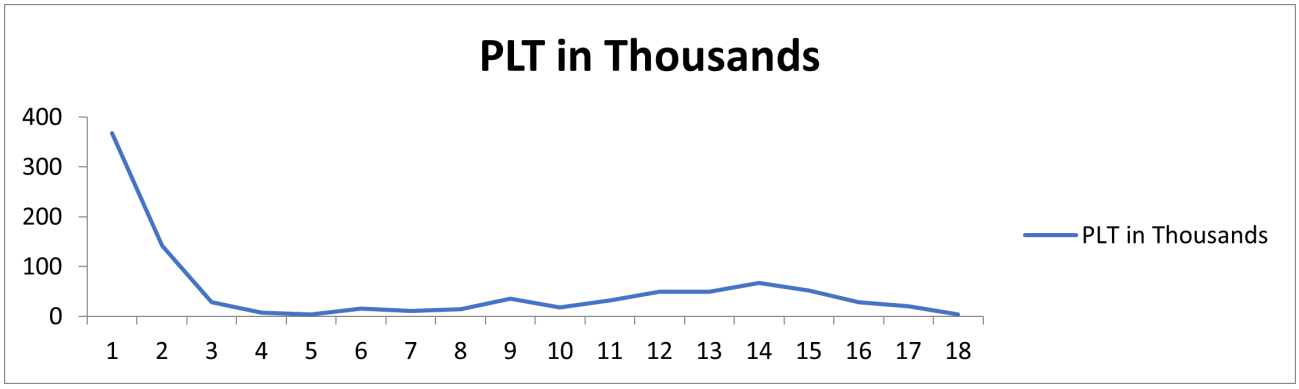
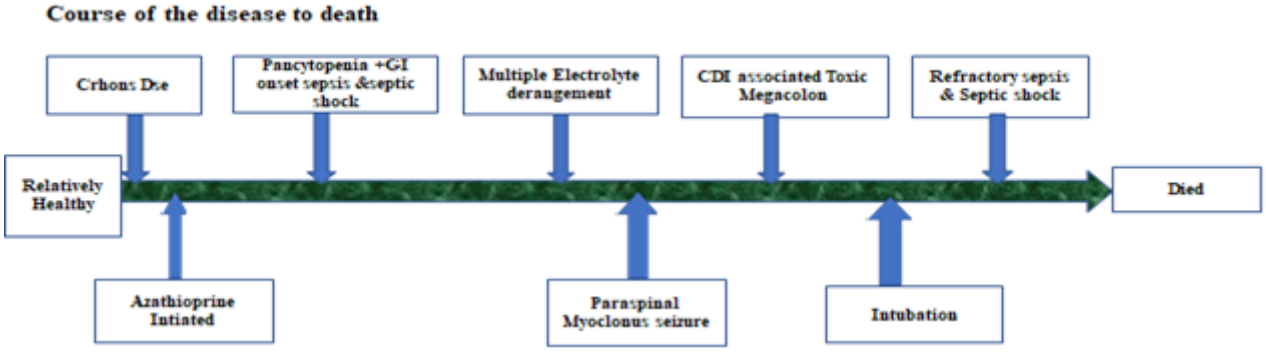


Figure 7. Pattern of Hemoglobin in young female crohn patient.





DISCUSSION

The prevalence of IBD increased substantially in many regions from 1990 to 2017, which might pose a substantial social and economic burden on governments and health systems in the coming years (1). IBD is becoming a growing health problem in Ethiopia. To date there are scanty reports from Ethiopia at a nationwide or hospital levels about the epidemiology and clinical characteristics of IBD. Hence treating physicians must have the necessary knowledge and skills on how to approach and provide timely and effective care for such patients. The major challenges encountered to do so far were late patient presentation, delay in diagnosis, lack of single or simple screening, diagnostic and monitoring test, and limited availability of treatment options, the potential negative consequences of toxic immunosuppressive and anti-inflammatory drugs. Majority of the patients with crohn disease usually diagnosed in their 20s and 30s (2). In our case, the patient was 23-year-old female patient who had been experiencing worsening of intermittent chronic watery diarrhea associated with right lower abdominal pain for the last one month. She used to have similar illness for the last three years. She went different nearby health facilities and was told to have typhoid fever on her most visits ,acute gastroenteritis, dyspepsia, acute appendicitis and something related to her reproductive organs on her other visits. She was not relived despite taking unspecified drugs.

Even though most of the recent studies show that among those with Crohn disease, 2.2% to 16.2% have a first-degree relative who also has the disease, there is no identified family with similar illness in our case. Patients who smoke tobacco and consuming diets composed of excessive sugar, fats, oil, and meat protein are at increased risk of acquiring the disease"(3, 4, 6). But in other studies , it is stated that the role of environmental factors either as the triggers or causes of the uncontrolled immune response continues to be debated(1).In our patient there were no smoking history and her stable diet was "Injera with wot".

A combination of endoscopic, histologic and radiologic and biochemical tests are required to diagnose crohn disease. Such diagnostic tools are not only they are fancy tests for the poor but also they are not commonly available. In sub-Saharan countries like Ethiopia where there are numerous causes of chronic diarrhea, diagnosing CD is very challenging. Patients are diagnosed lately after the disease progress to its severe stage. This was typically reflected in our case contributing the poor prognosis. It is not uncommon to misdiagnose and provide inappropriate treatment while patient condition is declining as revealed in our case.

A study done at Tikur Anbessa Hospital based at the capital city of Ethiopia revealed that the ileo-colon type was the most common disease phenotype (38%), and the inflammatory type was the most common disease behavior (49.3%) (8).

For the patient with moderate to severe CD like in our patient, first-line options for induction therapy include a biologic agent with or without an immunomodulator(eg, azathioprine (AZT), 6-mercaptopurine (6-MP), or methotrexate). For most patients with fistulizing moderate to severe CD (eg, perianal or intestinal fistula),combination therapy consisting of tumor necrosis factor-alpha (TNF) inhibitor (eg, infliximab) and an immunomodulator is indicated(5).Our previous clinical practice showed that 65.8%CD were on Steroid only, 1.4% were on immunomodulators(most on Azathioprine while the rest minority on Metotrexate or 6 Mercaptopurine). While 9.6% were on Steroid with immunomodulators, only 2.7% of patients used 5- aminosalicylic acids (5-ASAs) in the course of their illness. Despite the dramatic increase in use of biological therapy, none of the IBD patients were treated with biologic therapy (8).

Azathioprine is a synthetic purine analog resulting in inhibition of DNA, RNA and protein synthesis in the lymphocyte. AZT. Is the back bone of moderate to severe CD Rx used in a country with rampant Tb. when used as induction can be given empirically with gradual dosing and serial laboratory monitoring or dosing based on thiopurine-S-methyltransferase (TPMT) genotype or enzymatic activity (phenotype) testing(6). If TPMT testing is available, AZT should be initiated with low dose and adjust gradually. For the first 4 consecutive weeks, AZT should be given 50mg(50% of the ideal weight based therapeutic dose) by mouth with weekly monitoring of CBC, serum aminotransferases, total bilirubin, and amylase. If the patient is tolerating the drug, the white blood cell (WBC) count is >4000 cells/microL and the platelet count is ≥150,000/microL, increase the dose of AZA to 100 mg daily (6-MP 75 mg daily), provided that this dose is less than the maximum dose as determined by the patient's lean body weight, rather than the actual body weight (6). Myelosupression is Common and potentially lethal complication of azathioprine treatment. It occurs in the first 2-3 weeks of treatment and improves after a few weeks if the drug discontinued.

Our patient was induced empirically with AZT 100mg by mouth daily with prednisolone as an induction therapy. Her total WBC, hemoglobin and platelet level were normal. She developed pancytopenia after she took her medications for one month. She was progressively deteriorating which led her to be admitted to the medical intensive care unit after she was diagnosed as sepsis of GI focus with septic shock, moderate hypokalemia, mild hyponatremia, Crohn with acute flare, Pancytopenia with neutropenic fever. Though the causes of pancytopenia in IBD patient are multifactorial, The most likely causes in our patient are mainly high dose AZT and subsequent sepsis.

Intestinal TB is a close mimic of CD, and it is often difficult to differentiate the two diseases on the basis of clinical,

endoscopic, histological, and radiological characteristics. According to a report from India, significant numbers of patients have received a prior ant-Tb treatment. It indicated that 36.7% patients with CD and 7.8% with UC had received ant-Tb drugs before the diagnosis of respective disease was made(5).In our patient, Anti Tb was initiated at the time she experienced the refractory septic shock 5 days prior to her death.

High colectomy risk patients includes patients with extensive colitis, age less than 40years,admitted patients, patient with CDI and CMV, patient with High CRP and ESR and those requiring corticosteroids. Hence our patient could benefit if early surgical intervention was made.

CONCLUSION AND RECOMMENDATION

IBD as a disease of western countries now an obsolete view. Considering the progressive increase in crohn disease, a caring physician must address the multimodal crisis from such disease with vigilance. This case demonstrated that in high risk crohn patient, it is crucial to induce Azathioprine empirically in low dose with gradual escalation while monitoring CBC and LFT including bilirubin to prevent subsequent myelosupression. This case also revealed the need of early initiation of anti Tb in high patient in whom Tb and IBD cannot be differentiated. More over when a patient develop refractory septic shock with neuropenic fever, it may be wise consider Tb sepsis and manage accordingly while providing intravenous antibiotics with Granulocyte colony stimulating factor.

REFERENCES

1. S.Alatab,S.Sepanoulo, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, Lancet Gastroenterol Hepatol 2020; 5: 17–30 ,October 21, 2019.

2. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. http://dx.doi.org/10.1016/S0140-6736(17)32448-0.

3. Duricova D, Burisch, Jess T, Rousseau CG, Lakatos PL. Age-related differences in presentation and course of inflammatory bowel disease: an update on the population-based literature. Journal of Crohn's and Colitis. Vol. 8, 2014, pp. 1351-61.

4. Mazal J. Crohn disease: pathophysiology, diagnosis, and treatment. Radiologic Technology. 2014, pp. 297-316.

5. Jana Al H, Miguel R. Medical management of moderate to severe Crohn disease in adults, Uptodate , Mar 11, 2024.

6. Farrel.R., Overview of azathioprine and mercaptopurine use in inflammatory bowel disease, Uptodate , April 19, 2024.

7. Management of IBD Principles of internal medicine 22th edition.

8. Fekede N.,Berhanu Y. Sociodemographic features, Clinical characteristics and Treatment patterns of inflammatory bowel disease in patients seen at Tikur Anbessa Specialized Hospital, Addis Ababa University .January,2020.

9. Gary R. Lichtenstein, , Edward V. Loftus Jr. Kim L. Isaacs etal. America college of Gastrology clinical guideline: management of crohn disease in adults, March 2018.