according to the ACMG criteria[5]. This variant is predicted to cause loss of normal protein function through protein truncation and is also conserved across species. In silico analysis indicates that the effect of variant is damaging. The variant detected on exome sequencing was also verified by Sanger sequencing. Targeted Sanger sequencing in the younger sibling showed her to be homozygous for the wild variant. The CCDS sequence used for CARMIL2 is NM_001013838.3. HLA typing is planned so that the sibling can act as a donor for allogeneic hematopoietic stem cell transplantation[6].

Our case highlights both intestinal and extraintestinal manifestation of CARMIL2-deficiency, suggesting the role of immune regulation in intestinal homeostasis. This provides another critical example where PID can present with phenotypic characteristics of early onset-IBD and should be considered in differential diagnosis. Early diagnosis of CARMIL2 deficiency in VEO-IBD patients is critical to prevent fatal complications. We hope that our case enhances the recognition of the clinical manifestations of this recently recognized immunodeficiency and adds to the differential diagnosis of IBD in the pediatric population, especially if there are clinical signs and symptoms suggestive of T -cell deficiency/defects.

Conclusion

In conclusion, a detailed history and examination of extraintestinal manifestation can provide valuable clues, and genetic diagnosis is essential in cases of VEO-IBD to confirm the etiology. Though immunosuppressive therapy in CARMIL deficiency is helpful to tide over the crisis, a definitive hematopoietic stem cell transplant offers a gratifying response in the long term.

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Acute Pancreatitis, A Rare Non-Hematological Adverse Event in a Patient Treated with Inj. Carfilzomib for Relapsed Multiple Myeloma Post Autologous Stem Cell Transplant

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Carfilzomib is an epoxomicin derivate, which is used as an antineoplastic drug. Carfilzomib irreversibly binds to the 20S core subunit of the proteasome and inhibits it. This complex is primarily responsible for degrading a variety of cellular proteins. When carfilzomib binds to and inhibits this proteolysis, it results in accumulation of

poly-ubiquitinated proteins, which inhibits tumor growth by causing cell cycle arrest and induction of apoptosis.[1]

Carfilzomib is used as a second-line drug inpatients with relapsed multiple myeloma. The most common triplet regimen used to treat relapsed multiple myeloma is the KPD regimen (carfilzomib, pomalidomide, and dexamethasone).[2] The KPD regimen is administered as a 28-day cycle regimen. Inj. Carfilzomib is initiated at a 20 mg/m^2 dose on days 1 and 2 and increased to 27 mg/m^2 from day 8 onwards (days 8, 9, and days 15, 16). Carfilzomib is administered after dilution with 5% dextrose over 30 minutes. Prior oral or intravenous hydration is given depending on the tumor burden.[2]

Common adverse effects that occur in patients receiving intravenous carfilzomib are fatigue, nausea, thrombocytopenia, and leukopenia. Non-hematological adverse effects include dyspnoea, pneumonia, hypertension, cardiac toxicity, and hyponatremia. In clinical trials, one-third of the patients experienced mild to moderate dyspnoea without detectable lung injury, possibly because of the intravenous hydration prescribed.[3] An increase in serum pancreatic enzymes were reported by Nakamura et al in a patient receiving carfilzomib.[4] To the best of our knowledge based on an extensive literature search done using the Pubmed platform, this is the only second report describing acute pancreatitis after carfilzomib administration. This report will aid in creating awareness and help in the care of a patient presenting with such a rare complication.

Case Report

A-34-year-old female patient with relapsed IgG kappa multiple myeloma presented in June 2020. The diagnosis of multiple myeloma was made in 2016 upon evaluation of a right humerus fracture. She had received 6 cycles of VRD regimen (bortezomib, lenalidomide, and dexamethasone), after which she achieved complete remission. Subsequently, she underwent an autologous stem cell transplant (aHSCT) in 2017. Post aHSCT, she was on maintenance lenalidomide till 2019.

She had a relapse in 2020, when she developed a compression fracture of T3 vertebra and developed impingement syndrome. She received local radiotherapy (30 Gy) toT3vertebra, and chemotherapy using a VRD regimen from June 2020 to December 2020. There was no response post chemotherapy. She did not take any therapy from January 2021 to March 2021. On evaluation in March 2021, her laboratory parameters showed haemoglobin- 10.1 g/dl, total white cell count- 3300/mm^3, platelet count- 84,000/mm^3, serum creatinine- 1.43 mg/dl, serum calcium- 8.4 mg/dl, kappa free chain- 12,221 mg/dl, lambda free light chain- 5.1 mg/dl, kappa/lambda- 2381. A salvage chemotherapy using a KPD regimen was started in March 2021. Disease reassessment done after completion of 1 cycle showed partial response. She developed a fever on day 8 of cycle 2 of the KPD regimen and was diagnosed to have COVID19 infection. Day 8 chemotherapy was withheld in view of COVID infection and supportive treatment was continued at home. During home quarantine, her fever subsided within 72 hours and she was clinically stable without any symptoms. At the end of 3 weeks, repeat COVID PCR was negative and chemotherapy was resumed.

On the day of restarting chemotherapy, she complained of epigastric pain radiating to the back. Clinical examination was unremarkable except for mild tachycardia. On further evaluation, a diagnosis of acute pancreatitis was made. Serum pancreatic enzymes were elevated and USG abdomen showed bulky pancreas without any peri-pancreatic fluid collection, common bile duct dilatation, or gall stones. Laboratory parameters showed a progressive increase in serum pancreatic enzymes along with total count and C-reactive protein (CRP) as depicted in **Figure 1** .Conservative treatment was given, oral intake was stopped, and intravenous fluids and adequate analgesics were administered for pain relief. Serum calcium and vitamin D levels were normal. Serum triglyceride levels were mildly increased- 329 mg/dl. Inj. ceftriaxone was given empirically after obtaining blood for culture, procalcitonin, and C-reactive protein. Serum procalcitonin was normal and blood cultures did not show any growth. She required 3 doses of opioid analgesics to control pain on day 1. There was a low-grade fever noted on day 2 to day 4. Infectious causes of fever were ruled out. Etiological evaluation as advised by the gastroenterologist ruled out other possibilities. Clinical improvement in pain was noted from day 3 onwards and oral feeds were gradually resumed. Repeat USG abdomen (after 1 week) had shown bulky pancreatic tissue with normal common bile duct and normal gall bladder. Further chemotherapy was deferred by 2 weeks due to

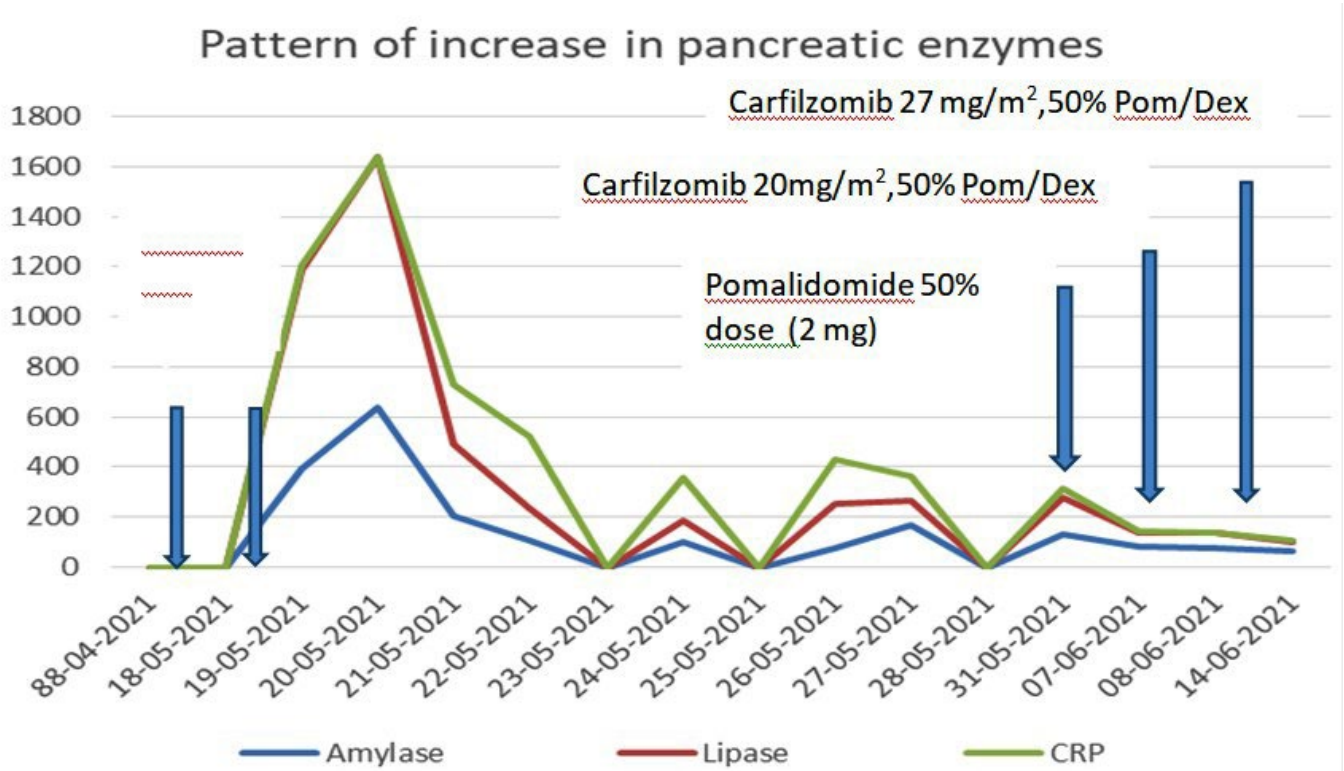

Figure 1: Patterns of increase in pancreatic enzymes (amylase and lipase) and inflammatory markers (CRP) with different doses of carfilzomib.

acute pancreatitis. It was resumed with a reduced dose of carfilzomib (20 mg/m^2) and a 50% dose of pomalidomide (2 mg) and dexamethasone (20 mg). She did not develop any symptoms with the adjusted dose of chemotherapy. Carfilzomib dose was increased to full dose after 1 week which she tolerated well.

Discussion

The KPD regimen is a very commonly used salvage therapy for relapsed multiple myeloma in post autologous stem cell transplant settings.[2] Oral pomalidomide is well tolerated and can lead to thrombocytopenia and neutropenia in a few patients. Hematological toxicity of carfilzomib includes anemia, thrombocytopenia, and neutropenia whereas non-hematological adverse events are hypertension, cardiac toxicity, and nephrotoxicity.[3] Pancreatic hyperamylasemia and hyperlipasemia associated with carfilzomib in multiple myeloma has been reported by Yuichi Nakamura et al.[4] Proteosome inhibitor-induced pancreatitis has also been reported.[5,6] Our case report shows similar findings of inflammation of the pancreas with increased pancreatic enzymes associated with classical clinical symptoms of pancreatitis.

In our case report, a prior COVID-19 infection could possibly be a confounding factor. Literature search showed few reports of pancreatitis post COVID19 infection, additionally, there are no reports of pancreatitis due to pomalidomide. Our patient developed symptoms that fulfilled the criterion of mild pancreatitis and was managed conservatively.

Conclusion

Although very uncommon, acute pancreatitis can be a cause of abdominal pain after administration of Inj. carfilzomib in a patient with multiple myeloma. A high index of suspicion is required for timely diagnosis and intervention. The drug can be re-challenged in reduced doses after recovery from pancreatitis, and dose escalation can be done based on tolerability.

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Co-morbidity of Cystic Fibrosis and Celiac Disease in an Indian Female Child

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Cystic fibrosis (CF; OMIM: 219700), is an autosomal recessive disease caused by the homozygous or compound heterozygous mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (OMIM*602421) encoding the CFTR protein. It is the most common lethal genetic disease among Caucasians, with a reported birth prevalence of 1:2000-1:4000 live births. The CFTR dysfunction affects epithelial cells, compromising innate and adaptive immune systems both in terms of quality and quantity of response resulting in immunological imbalance; which provides the basis for developing autoimmune diseases (AID) as comorbid conditions. In CF, the most investigated AID is celiac disease.[1]

The risk of the co-morbidity of CF and CD has also been suggested previously. The incidence of the two conditions occurring in the same patient has been estimated to be 1 in 2,000,000-1:5,900,000. Several case–control studies reporting a wide range (1.2-2.13%) of proven CD incidence in European CF patients have been published in the last decade[2].

We report a case in which the female child was diagnosed with this co-morbidity at 14 years of age. We conclude that despite the different pathophysiology, both CF and CD cause malabsorption; and pose a diagnostic dilemma for pediatricians in distinguishing between CF-related or potentially CD-related GI symptoms. A better understanding of the comorbidity of both diseases is needed for early diagnosis and management.

Case Report

A 14 Years old female child, known patient of celiac disease for the last 10 years; on a gluten-free diet, presented with complaints of recurrent respiratory infections, undocumented fever in the last year and cough in the last 6 months. Fever had a diurnal variation with evening rise of temperature and was aggravated in the last 20 days. Cough was mucoid, greenish-colored, non-blood stained, and associated with respiratory difficulty and fever. She also has a history of oily stools, constipation and failure to gain weight. The patient kept on taking medications from various pediatricians with symptomatic relief only.

She was hospitalized at 3 years of age for cough and respiratory distress at 4 years of age with complaints of constipation and surgery for bowel obstruction, and at 7 years of age for cough, fever and blood transfusion. Her mother's younger sister was also diagnosed with celiac disease. Her antenatal course was uneventful but there was history of meconium-stained liquor. She was given mixed feeding and weaning was started at 7 months. She is incompletely immunized. Currently, she is taking milk, makhane, cornflakes, 2 chapatis of celiac flour, vegetables, dal and tea.