Medical Science Sample

Case Report

Acute Appendicitis Masquerading as Distal Intestinal Obstruction Syndrome in Adult Cystic Fibrosis

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Overshadowed by sino-pulmonary infections, Cystic Fibrosis (CF) commonly affects gastrointestinal organs because of secretory and motility dysfunction. Infrequently, the resulting changes can result in the Distal Intestinal Obstruction Syndrome (DIOS), an increasingly diagnosed gastrointestinal condition in adult CF patients. We present the case of a 22-year-old male who presented to our hospital with right lower quadrant abdominal pain. Despite the suspicion of acute appendicitis, the patient was subsequently diagnosed with DIOS. Our case highlights the importance of considering DIOS as a differential diagnosis for right lower quadrant abdominal pain in CF patients, especially for physicians working at community hospitals that may not have a CF care program available.

1. Introduction

Cystic Fibrosis (CF) is a genetic disease that affects multiple organs. With the advancements in the management of CF patients, patients can now often survive to adulthood. However, the improved life expectancy among adult CF patients has led to an increase in extrapulmonary, notably gastrointestinal, manifestations, which were previously uncommon. Distal Intestinal Obstruction Syndrome (DIOS) continues to be a rising complication in adult CF patients, presenting acute abdominal pain mimicking an acute abdominal emergency.

2. Case Report

A 22-year-old Turkish-origin male with a past medical history of Cystic Fibrosis presented with a one-day history of right lower quadrant abdominal pain. He described a sharp periumbilical pain that continued to worsen, which then shifted to the right lower quadrant of the abdomen. Prior to the onset of the abdominal pain, he reported experiencing nausea and anorexia for three days. His last bowel movement was two days prior.
days prior to admission. Upon reviewing the patient’s past history, it was noted that he had several episodes of pneumonia, for which he was appropriately treated with antibiotics. Notably, no history of constipation or recurrent abdominal discomfort was reported prior to this. At home, the patient was prescribed Albuterol inhalations as needed, Dornase Alfa inhalations, Aztreonam lysine nebulization, 500 mg Azithromycin three times a week, Lansoprazole, Lumacaftor-ivacaftor twice a day, Lipase-protease-amylose capsule three times a day, and a multivitamin capsule once a day. The patient was also diagnosed with Cystic Fibrosis (CF) at the age of four, and this disease progressed to exocrine pancreatic insufficiency, which was being treated with pancreatic enzymes. On abdominal examination, he was found to have had diminished bowel sounds and tenderness on right lower quadrant with equivocal rebound tenderness on the right lower quadrant. Laboratory analysis showed leukocytosis (white blood cell count (WBC) 13.0 mm/KL neutrophils count, 62%) with a normal differential. He had no electrolyte imbalances. Computed Tomography (CT) of the abdomen revealed thickening, and edema around the terminal ileum, inflammatory changes in the colon with inflammatory changes, free fluid in the right paracolic gutter adjacent to the cecum, an appendix measuring 5.3 x 4.6 mm, and reactive lymph nodes (Figures 1 and 2).
FIGURE 1: Axial abdominal computed tomography scan depicting thickening around the terminal ileum and colon (yellow arrows) along with extraluminal fluid and reactive lymph nodes.

FIGURE 2: Coronal view computed tomography scan showing thickening of the ileum with a distended appendix (yellow arrows).

measuring 5.3 x 4.6 mm, and reactive lymph nodes (Figures 1 and 2). Due to extraluminal fluid and cecal wall edema with inflammation, early acute appendicitis could not be excluded as a possible diagnosis. Surgical intervention was performed required, which revealed a ruptured microperforation of a cecal diverticulum and a distended appendix in chronic adhesions, for which he required an appendectomy and partial cecectomy with an intact ileocecal valve (IC valve). Postoperatively, he was diagnosed with DIOS and was subsequently started on Polyethylene Glycol. The patient made an unremarkable recovery and was discharged home. He was followed up in the...
outpatient clinic without and did not have any recurrence of any symptoms.

3. Discussion

Distal Intestinal Obstruction Syndrome (DIOS) was previously called known as Meconium Ileus-equivalent in the past, described is characterized by the collection of viscid fecal material within the lumen combined with sticky mucoid intestinal content adherent to the intestinal wall of the terminal ileum and cecum [1]. Perez-Aguilar et al. reported the prevalence of DIOS was 19.5% (mean age 20.6 years) among 46 CF patients in a retrospective analysis, while Dray et al. conducted a cross-sectional study reporting a 15.8% (mean age 28.9 years) prevalence among 171 CF patients in a cross-sectional study [2, 3]. Despite the though there continues to be a limited assessment of the prevalence of DIOS in adult CF patients, DIOS is considered more common among adults compared to children due to because of increased disease progression.

Defective intestinal chloride and water secretions into the gut, luminal acidity, and loss of bile salt all contribute to the_
development of DIOS [1]. These patients characteristically present with right lower quadrant pain, nausea, abdominal distension, and failure to pass stools or flatus [1, 3]. In some patients, a palpable right lower quadrant mass can be appreciated present that may be confirmed on abdominal X-ray [1]. Though abdominal X-rays are recommended to aid in the diagnosis of DIOS, they are inadequate in differentiating ileus from other causes of abdominal pathologies that may present in Cystic Fibrosis CF patients [4].

Due to the proximity of the anatomical locations, as well as the overlapping clinical presentations, appendicitis and intussusception may mimic DIOS, which further leads to diagnostic uncertainty. Overlap of several intra-abdominal pathologies in CF increases the risk of misdiagnosis, especially with acute appendicitis, as these patients’ underlying pathologies may be masked in patients with pulmonary infections using antibiotics [5, 6].

Osmotic laxatives are the cornerstone of bowel regimens for the treatment of DIOS. The most commonly prescribed laxative is Polyethylene Glycol (PEG) administered at a dose of 20–40 ml/kg/h up to a maximum of 1 L/kg/h for a total of 8 hours, resulting in achieving fecal effluent consisting of clear fluid, along with the resolution of abdominal pain and constipation [1, 6]. If the diagnosis remains unclear, and thus, requires surgical intervention, ileocecal valve resection should be considered to prevent the development and recurrence of intestinal obstruction sequelae and growth, especially in adolescents [7].

With the increase in immigration of foreigners into the USA, inner-city and community hospitals may not be sufficiently equipped with a Cystic Fibrosis CF care center; moreover, nor may these hospitals have programs in provision, with expertise available to other clinicians involved in patient care.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

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All authors contributed to the revision and approval of the manuscript.

References


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Life Sciences Sample

Case Report

Methylmalonic Acidemia with Novel MUT Gene Mutations

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A 5-years-old boy presented with recurrent episodes of fever, feeding problems, and lethargy, since the age of 11 months, and poor weight gain. He was admitted to our hospital and evaluated for metabolic disorders; subsequently, he was diagnosed with methylmalonic acidemia (MMA). He was treated with vitamin B12 and carnitine supplements and has been on follow-up for the last 3 years. Mutation analysis by next generation sequencing (NGS), supplemented with Sanger sequencing, revealed two novel variants in exon 5 and exon 3 of the MUT gene responsible for methylmalonic acidemia (MMA). Recently, he had developed dystonic movements including orofacial dyskinesia. With the advent of NGS, judicious use of NGS with Sanger sequencing can help identify causative and possibly pathogenic mutations.

1. Case Presentation

A 5-year-old child presented for the first time at the age of 11 months, with complaints of fever, vomiting, poor feeding, and lethargy for the first time at the age of 11 months. We observed that the patient had pallor and tachypnea and was drowsy. Further evaluation was suggestive of high anion-gap metabolic acidosis with ketonuria (urine ketones 3+) and with normal electrolytes, blood sugar (94 mg/dL), vitamin B12, and homocysteine levels. Plasma ammonia and plasma lactate were 118 units, and plasma lactate was 2.9 units, respectively. Transcranial magnetic stimulation TMS results were normal, but gas chromatography mass spectrometry analysis of but urine GCMS revealed elevated 3-OH propionic acid [12.39 retention time (RT)] as well as elevated methyl malonic acid levels [16.92 RT, Suppl Figure 1, in Supplementary Material available online at https://doi.org/10.1155/2017/8984951]. Since then, the child was on a low-protein diet, and carnitine, biotin, thiamine, and vitamin B12 injections. The child was thereafter admitted to the hospital on seven multiple occasions (7 times) with acute decompensation and managed as per protocol. Mutational analysis was sent for methylmalonic acidemia (MMA) which showed a single heterozygous missense variant c.976 A>G (p.Arg326Gly) in exon 5 of the MUT gene (genomic coordinates: chr 6: 49421405): a variant of uncertain significance. Chromosomal microarray analysis did not reveal any major deletion or duplication which could disrupt the gene. Since exon 3 and exon 6 were not adequately covered by next generation sequencing (NGS), further evaluation by Sanger sequencing for targeted exons was performed, and a second mutation in exon 3 c.753 G>A (p.=) was identified. The variants were predicted as found to be damaging by the SIFT database score (Suppl data) and as they were also predicted to be deleterious by Polyphen-2 and Mutation-Taster. 

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they were absent not found in the ExAC database. Brain magnetic resonance image MRI brain of the patient (done at the age of four years) was showing multifocal cystic encephalomalacic changes with surrounding gliosis in deep white matter predominantly in frontoparietal regions (Figure 1). During the latest admission of the patient to the hospital, we observed child was found to have fresh neurological findings in the form of perioral tremors, generalized hypertonia, and generalized dystonia with clonus with exaggerated deep tendon reflexes. The patient was treated with intravenous dextrose and sodium bicarbonate and was continued on carnitine and injection of vitamin B12. Plasma ammonia and plasma lactate were 18 units and 4.9 units, respectively. Brain magnetic resonance image MRI brain of the patient was repeated and revealed bilateral basal ganglia hyperintensities, suggestive of metabolic stroke. After the subsidence of acute crisis, he was discharged on carnitine, injection of vitamin B12, and trihexyphenidyl. His parents were counseled regarding the prognosis and for prenatal diagnosis for next subsequent pregnancies.

2. Discussion

MMA presents with lethargy, acidosis, hypoglycemia/ hyperglycemia, ketosis, and recurrent episodes. MMA due to MUT gene mutations usually leads to severe phenotypes due to MUT gene mutations, and around 35–40% of cases are due to novel mutations [1, 2]. There can be Missense or nonsense mutations, deletions, insertions, and so on in the MUT gene and so on can leading to a clinical phenotype.

The advent of NGS technology has enabled better characterization of mutations in several populations. However, Sanger sequencing remains a useful adjunct in molecular testing in these cases. It is required to find mutations when there is a strong clinical suspicion for them. Sometimes in NGS, due to because of incomplete coverage of the exons by NGS, Sanger sequencing is required to find mutations, if there is strong clinical suspicion. In this study, by using both the techniques, we could found the two MUT...
variants responsible for MMA in the patient's clinical condition. In a Saudi study on 60 patients of MMA, nonsense, missense, and frameshift mutations were detected across the MUT gene [3]. Another study in 43 Chinese patients identified 8 recurrent mutations and 10 novel mutations [4]. A previous Indian study in 15 patients with clinically diagnosed MMA identified one novel exon 12 mutation in the MUT gene with predicted pathogenicity. In this case, we identified two novel variants, one in exon 3 and another in exon 5 of the MUT gene. Both were labelled as variants of unknown significance (VUS). The exon 3 variant is a synonymous variant, and a different nucleotide change c.753 G>C (p.Lys251Asn) has been reported earlier in ClinVar. Some synonymous variants can also affect the splicing or protein function and lead to clinical phenotypes. The identified exon 5 variant is novel, but another close variant c.977 G>A (p.Arg326Lys) has been reported in ClinVar. The variants were found to be deleterious on bioinformatic analysis and were absent not found in the ExAC database. Both variants identified in the present case could possibly explain the phenotype of MMA in the child. MUT-related MMA has poor prognosis in most cases. Specialized diet and supplements may not improve the outcome, even if MMA is diagnosed early. Early recognition and appropriate treatment of acute crises are necessary. Metabolic stroke can sometimes occur in the absence of acute metabolic decompensation, so meticulous neurological examination at every visit is useful. The treatment options for therapy include early liver transplantation [5] and possibly gene therapy in the future. Genetic counseling and prenatal diagnosis could help these families of the patients in making reproductive decisions.
Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References


Abstract

The present paper reports the use of $^{31}$P NMR spectroscopy to predict the isomer structures of [bis-4-methoxy-phenyl-[3-(4-methoxy-phenyl)-allylidene]-amino]-bis(triphenylphosphine)ruthenium(II), also known as bis(di-p-anisole)-1,4-azabutadiene-bis[triphenylphosphine]ruthenium(II), complexes. The complexation reaction was carried out using (di-p-anisole)-1,4-azabutadiene (compound 1), triphenylphosphine, and ruthenium chloride in 2:2:1 ratio under refluxing conditions for five hours. The formation of the complexes was further confirmed by characterization using FTIR and UV–Vis spectroscopy to support the formation of ruthenium(II) complexes. The results of $^{31}$P NMR spectroscopy study on ruthenium(II) complexes suggested that there are three isomers present after the complexation reaction.

Keywords: NMR, nuclear magnetic resonance; structural prediction; Bisbis(di-p-anisole)-1,4-azabutadiene-bis[triphenylphosphine]ruthenium(II); $^{31}$P NMR spectroscopy.
1. Introduction

Nuclear magnetic resonance (NMR) spectroscopy is an essential instrument in analytical tools in the field of chemistry as it helps determine elucidate the structure of a molecule. Furthermore, it can be used to identify impurities in a sample and determine the rate of formation and degradation of a compound. Even in the 1970s, NMR has been used to determine the cancer formation which was identified to be a simple, fast, and low-cost method for this purpose.

As part of our long-term research into the synthesis of ruthenium(II) complexes, we used the (di-p-anisole)-1,4-azabutadiene (I) and triphenylphosphine (PPh3) as the ligands to prepare reaction complexes with ruthenium trichloride under reflux conditions. The resulting products were formed, were checked analyzed by using 31P NMR spectroscopy, and the spectral observations found in the spectra are worth being discussed in the present communication.

For inorganic inorganic chemistry, commonly used is 31P NMR spectroscopy to identify the structure of a complex containing phosphine ligands as a common method.[4, 5] For example, this technique has been used to determine the mechanism of Wilkinson hydrogenation based on identifying the coupling patterns among the phosphine ligands as well as their coupling constants between the phosphine ligands and the rhodium(I) metal.[6]

2. Methodology

The ruthenium complexes were characterized using UV–Vis, FTIR, and 31P NMR spectroscopies. The IR spectra were recorded using a Thermo Scientific Nicolet iS10 spectrophotometer using KBr discs.

The 1H NMR spectrum of compound I and 31P NMR spectrum of the ruthenium(II) complexes were recorded using a JEOL INX-500 spectrometer with TMS as the internal standard. The absorption spectra were recorded using a Jasco V-630 UV–Vis spectrophotometer.

2.1 To prepare Preparation of 4-[4-(methoxyphenyl)-3-[4-(methoxy-phenyl)-allylidene]-amine or (di-p-anisole)-1,4-azabutadiene (I)

A 4-methoxyphenyl aldehyde methoxyacetaldehyde (1.62 g, 10.00 mmol) was dissolved in 10 mL of ethanol, and followed by the addition of 4-methoxyniline (1.23 g, 10.00 mmol), which was then added to solution. The reaction mixture was stirred and to obtain a resulted in green-yellow solid, which was filtered, washed with 5 mL of ethanol and dried in vacuo. The solid was purified by dissolving it in DCM and layered with hexane via slow diffusion. Yield: 2.368 g (88.7%). IR (KBr, cm−1): 3034 (C-H stretching), 1627 (C=N stretching), 1601 (C=C stretching, aliphatic), 1575 and 1468 (C=C stretching, aromatic), and 1110 (OCH3 stretching), 1661 (C=N), 1576 (C=N), 1469 (C=C stretching of aromatic ring), 1341 (C=O), and 29.9 (s, 1P); UV–Vis (DCM, λmax): 273, 337; Anal. Calc. for C17H14O2N2 (%) C, 76.38; H, 6.41; N, 5.24; Found (%): C, 76.75; H, 6.31; N, 5.05.

To prepare 2.2 Preparation of bis(4-methoxy-phenyl)bis[4-(methoxy-phenyl)-allylidene]-amine]bis(triphenylphosphine)triruthenium(II) or bis[(di-p-anisole)-1,4-azabutadiene-bis(triphenylphosphine)ruthenium(II)] Complexes Complexes

RuCl3·3H2O (2.070 g, 1.00 mmol) and PPh3 (0.525 g, 2.0 mmol) were added to a round-bottom flask containing 10 mL of ethanol, and the mixture was then refluxed. Compound I (0.316 g, 2.0 mmol) was then added to the round-bottom flask, and the mixture was refluxed again. The resulting pale-maron solids were washed, filtered and washed with hexane, and the precipitate was dried in vacuo: IR (KBr, cm−1): 3034 (C-H stretching), 1661 (C=N), 1576 (merged IR band for aliphatic and aromatic C=C stretching from aliphatic and aromatic), 1469 (C=C stretching of aromatic ring), and 654 (Ru-C) and 577 (Ru-N), 31P NMR (202.5 MHz, CDCl3): 49.7 (d, 1P, Hz), 47.4 (d, 1P, Hz), 41.7 (d, 1P, Hz), 39.7 (d, 1P, Hz), 35.1 (s, Ph,P=O), and 29.9 (s, 1P); UV–Vis (DCM, λmax): 321 and 382.

3. Results and Discussion

The characterization of the ruthenium complexes was characterized using the UV–Vis, FTIR,
The absorption spectra of the ruthenium complexes (Fig. 1) show the presence of two pairs of doublets and one singlet, indicating the presence of three isomers (1:1:1 ratio) present during the complexation reaction with the ratio of 1:1:1.

Figure 1: 31P NMR spectrum for of ruthenium(II) complexes.

The singlet at 29.88 ppm reveals that the two PPh units are magnetically equivalent in the ruthenium(II) complex. The two PPh units are either located at the axial position and are, which is trans to each other (Fig. 2(a)) or located in the equatorial plane which is only trans to one of the C atoms from the C=C bond. In contrast, the two PPh units are magnetically equivalent in the equatorial plane (Fig. 2(b)).

Figure 2: Postulated structures of (a) trans- and (b) cis-bis(p-diamino)-1,4-azabutadiene]-bis(triphenylphosphine) ruthenium(II).

Meanwhile, the pair of doublets at 41.84 and 39.74 ppm with a coupling constant of 21 Hz is assigned to the cis isomer of the ruthenium(II) complex, as shown in Fig. 3(a). Lastly, another pair of doublets at 49.80 and 47.36 ppm with a coupling constant of 38 Hz is assigned to the trans-ruthenium(II) complex (Fig. 3(b)).

Figure 3: Postulated structures of (a) cis- and (b) trans-bis(p-diamino)-1,4-azabutadiene]-bis(triphenylphosphine) ruthenium(II).

On the other hand, the binding of compound 1 to the ruthenium(II) metal center might be confirmed using FTIR and UV-Vis spectroscopy. Comparison of the IR spectra between compound 1 and the ruthenium complex (Fig. 4) reveals that the vibrations of C-N and C=C stretching bands have been shifted after binding to the ruthenium(II) metal center. The IR C=N stretching band is shifted from 1627 cm⁻¹ in the spectrum of compound 1 to 1661 cm⁻¹ in the spectrum of the ruthenium complex [9, 10]. In contrast, whereas the IR C=C stretching band appears at 1601 cm⁻¹ in the spectrum of compound 1, it is not clearly shown in the spectrum of the ruthenium complex because the IR bands of aliphatic and aromatic C=C bonds for aliphatic and aromatic moieties merge into one single broad IR band centered at 1576 cm⁻¹. Nevertheless, the two additional IR peaks appear at 577 and 654 cm⁻¹ in the fingerprint region of the spectrum [9, 10] indicating the formation of the respective Ru-N and Ru-C bonds [11].

Figure 4: IR spectra of (a) compound 1 and (b) ruthenium(II) complexes.

The complexation of compound 1 to the ruthenium(II) metal center is further supported by the UV-Vis data spectra as shown in Fig. 5. Even in the case of compound 1, two absorption bands are observed at 273 and 372 nm, which are assigned to the transition of the benzene ring and azabutadiene group [12], respectively. After the complexation, both absorption bands show significant shifts to 321 and 382 nm, respectively, demonstrating the significant shifts of these two absorption bands that have proven compound 1 was successfully bound to the ruthenium(II) metal center via the nitrogen atom from the C=N group and the carbon atom from the aliphatic C=C aliphatic group of the C=C-C=N moiety.
Figure 5: UV-Vis spectra of (a) compound 1, (a) and (b) ruthenium (II) complex (b).

4. Conclusion

Based on $^{31}$P NMR spectral evidence, we confirmed from $^{31}$P NMR spectrum has shown the presence of three isomers of the bis(di-p-anisole)-1,4-azabutadiene-bis(triphenylphosphine)ruthenium(II) complex in the 1:1:1 ratio of 1:1:1. In addition, the data from IR and UV-Vis spectral data revealed the successful binding of compound 1 has bound to the ruthenium(II) metal center.
References