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

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Overshadowed by sino-pulmonary infections, with the improved life expectancy in Cystic Fibrosis (CF) patients, there has been an increase in gastrointestinal manifestations because of secretory and motility dysfunction. Infrequently, these changes can result in 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, with the suspicion of acute appendicitis, the patient and was subsequently diagnosed as 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 which may not have a CF care program available.

1. Introduction

Cystic Fibrosis (CF) is a genetic disease of that affects multiple organs. With advancements in the management of CF patients, patients can now often survive to adulthoods [1]. However, the improved life expectancy among adult CF patients has given rise to an increase in extrapulmonary, notably gastrointestinal, manifestations, which did not happen previously uncommon. Distal Intestinal Obstruction Syndrome (DIOS) continues to be a rising complication in adult CF patients, presenting acute abdominal pain like and mimicking an acute abdominal emergency.

2. Case Report

A 22-year-old Turkish-origin male with a past medical history of CF 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 to admission. The patient was also diagnosed with CF at the age of four, and the disease progressed to exocrine
Pancreatic insufficiency, which was being treated with pancreatic enzymes. 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 inhalation as needed, Dolase, Alfa inhalation, 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 at the age of four and his disease progressed to exocrine pancreas 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/L, 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 5.3x4.6 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 with 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, 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 to be followed up in the outpatient clinic without and did not have any recurrence of any symptoms.

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Due to the improved life expectancy of CF patients, DIOS is now being increasingly diagnosed in adult patients with CF. Distal Intestinal Obstruction Syndrome (DIOS) was called a Meconium Ileus equivalent in the past, described 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 that 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 in 171 CF patients in a cross-sectional study [2, 3]. Despite the limited assessment of DIOS in adult CF patients, DIOS is considered more common among adults compared to children due to increased disease progression.

Distal Intestinal Obstruction Syndrome (DIOS), previously known as a Meconium Ileus equivalent, in the past, described 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]. 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 may be appreciated that may be confirmed on abdominal radiography [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. This further leads to diagnostic uncertainty. Overlap of several intra-abdominal pathologies in CF increases the risk of misdiagnosis, especially with acute appendicitis, as these patient's underlying pathologies may be masked in CF patients with pulmonary infections using antibiotics, as seen in our case [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 America, inner-city and community hospitals may not be sufficiently equipped with a Cystic Fibrosis CF care center; moreover, these hospitals may not have programs in provision, with expertise available to other clinicians involved in patient care. Therefore, our case highlights the significance of considering DIOS as a differential diagnosis in CF patients presenting with right lower quadrant abdominal pain, particularly in hospitals without a CF care program available.

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-year-old boy presented with poor weight gain and 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, because and was diagnosed with methylmalonic acidemia (MMA). He was treated with vitamin B12 and carnitine supplements and has been followed up for the last 3 years. Mutation analysis by next generation sequencing (NGS), supplemented with Sanger sequencing, revealed two novel mutations in exon 5 and 3 of the MUT gene responsible for the methylmalonic acidemia (MMA) in exon 5 and exon 3. Recently, he developed dystonic movements, including orofacial dyskinesia. With advent of NGS, judicious use of NGS along with Sanger sequencing can help in identification of causative possibly-pathogenic mutations responsible for various clinical conditions and can help in early diagnosis and appropriate treatment of the conditions.

1. Case Presentation

A 5-year-old boy. The child presented for the first time at the age of 11 months, presented with recurrent complaints of fever, vomiting, poor feeding, and lethargy since the age of 11 months. On examination, we observed that the patient had pallor and tachypnea and was drowsy. Laboratory tests further evaluation suggested that the patient had witnessed 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)] and 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 patient 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), as a variant of uncertain significance. Chromosomal microarray analysis done did not reveal any major deletion or duplication that 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 done, and a second and
The patient was treated with intravenous dextrose and sodium bicarbonate and was continued on carnitine and injection of vitamin B12, injections. Plasma ammonia and plasma lactate were 18 units and lactate level was 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, injections, 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 lead 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 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. By careful use of both techniques, we could found the two MUT variants responsible for MMA in the patient. Previously, in a Saudi study on 60 patients of MMA patients, 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 in the MUT gene [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, and 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 not found in the ExAC database. Both variants identified in the present case could be responsible for possibly explain the phenotype of MMA phenotype in the child. MUT-related MMA has poor prognosis in most cases. Specialized diet and supplements may not improve the outcomes, 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; thus, meticulous neurological examination at every visit is important. The treatment options for MMA for therapy include early liver transplantation [5] and possibly-gene therapy could also be used in the future. Genetic counseling and prenatal diagnosis could help the families of the patients in making reproductive decisions in the future.
Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors would like to acknowledge Dhiti Omics Tech–nologies Pvt Ltd for assistance help in mutation analysis.

References


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In this study, 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)] complex, also known as bis(di-p-anisole)-1,4-azabutadiene-bis[triphenylphosphine]ruthenium(II), complex, was synthesized using refluxing conditions of (di-p-anisole)-1,4-azabutadiene (compound 1), triphenylphosphine ($PPh_3$), and ruthenium chloride in the ratio of 2 : 2 : 1 for five hours. The formation of the ruthenium(II) complex was confirmed by FTIR and UV–Vis spectroscopic analysis to support the formation of ruthenium(II) complexes. $^{31}$P NMR spectroscopy study on ruthenium(II) complexes suggested the presence of three isomers present after the complexation reaction.

Keywords: $^{31}$P NMR spectroscopy; FTIR spectroscopy; UV–Vis spectroscopy; Ru complex; Isomers; Structure prediction

1 NMR, nuclear magnetic resonance; FTIR, Fourier transform infrared; UV–Vis, ultraviolet–visible
1. Introduction

Nuclear magnetic resonance (NMR) spectroscopy is an essential instrument analytical tool in the field of chemistry as it helps determine elucidate the structure of a molecule, identify detect the presence of impurities in a sample, and determine the rates of formation and as well as degradation of a compound. Even in 1970s, NMR has been used as early as in the 1970s, already been used to determine detect the cancer formation which was identified to allow a simple, fast, and low-cost method so for this purpose identify cancer formation [1–3].

For Inorganic Chemistry, commonly, using 31P NMR spectroscopy, to identify the structure of a complex containing phosphine ligands is very common [4, 5]. For example, the well-known example is the use of 31P NMR spectroscopy to determine the mechanism of Wilkinson hydrogenation was determined by 31P NMR spectroscopy, mechanism based on by identifying the coupling patterns among the phosphine ligands as well as those and also the coupling constants between the phosphine ligands as well as the rhodium(I) metal center also [6].

As part of our long-term research interest in the synthesis of ruthenium(II) complexes synthesis, we used (di(p-anisole)-1,4-azabutadiene) (I) and triphenylphosphate (PPh3) as the ligands to, for reaction between with ruthenium trichloride under reflux condition. The structures of the product resulting complexes were formed, were checked identified by using 31P NMR spectroscopy, FTIR spectroscopy, and UV-Vis spectroscopy and the results found in The spectra are worth to be discussed in the present communication. For inorganic chemistry, using 31P NMR to identify the structure of a complex containing phosphine ligands is very common [4, 5]. The well-known examples is the use of 31P NMR spectroscopy to determine the Wilkinson hydrogenation mechanism by identifying the coupling patterns among phosphine ligands and also the coupling constants between phosphine ligands as well as the rhodium(I) metal center [6].

2. Methodology

The ruthenium complexes were characterized using UV-Vis, FTIR, and 31P NMR spectroscopy. The IR spectra were recorded using a Thermo Scientific Nicolet iS10 spectrophotometer in using KBr discs. The 1H NMR spectrum of compound I and 31P NMR spectrum of the ruthenium(II) complexes were recorded using a JEOL JNM-ECX 500 spectrometer with TMS as the internal standard. The absorption spectra were recorded using on a Jasco V-630 UV–Vis spectrophotometer.

2.1. Preparation of (4-Methoxy-phenyl) [3-(4-methoxy-phenyl)allyl]dineamine or (di p-Anisole)-1,4-azabutadiene(I)

4-Methoxy-cinnamaldehyde (1.62 g, 10.00 mmol) was dissolved in 10 mL of ethanol, and followed by the addition of 4-methoxynitromethane (1.30 g, 10.00 mmol), which was then added to solution. The reaction mixture was stirred and to obtain a result in green-yellow solid. The solid was filtered, washed with 5 mL of ethanol, and dried in vacuo. The solid was purified by dissolving it in DCM and then in DCM and then refluxed with hexane via slow diffusion. The product obtained yield: 2.368 g (88.7%); IR (KBr, cm−1) ν 3036 (C-H stretching), 1627 (C=N stretching), 1601 (C=C stretching, aliphatic), 1575 and 1468 (C=C stretching, aromatic), and 1110 (OCH3 stretching). δ1H NMR (500 MHz, CDCl3) δ 8.25 (d, 1H, H-2, C=H=N), 7.47 (d, 2H, H-2), 7.18 (d, 2H, H-2), 7.05 (t, 1H, H-2, C=H=N), 6.90 (m, 1H, H-2, C=H=N), 6.09 (d, 4H, H-3), 3.83 (d, 3H, H-3), and 3.87 (s, 3H, OCH3). The 1H NMR spectrum (DCM, δppm) 273, 373; Anal. Calc. for C20H15O(N): C, 76.38; H, 6.41; N, 5.24; Found (%): C, 76.35; H, 6.31; N, 5.05.

2.2. Preparation of Bis-(4-Methoxy-phenyl)[3-(4-methoxy-phenyl)allyl]dineamine or (di p-Anisole)-1,4-azabutadiene-bis(triphenylphosphate)ruthenium(II) Complexes

For the synthesis of bis(di-p-anisole)-1,4-azabutadiene-bis(triphenylphosphate)ruthenium(II) complex, RuCl3·3H2O (2.07 g, 0.43 mmol) and PPh ₃ (0.525 g, 2.0 mmol) were added to a round-bottom flask containing 10 mL 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-gray maroon solids were washed and the pH was titrated was then dried in vacuo: IR (KBr, cm−1) ν 3034 (C-H stretching), 1611 (C=N), 1576 (emergent IR band of aromatic and aliphatic C=C stretching from aliphatic and aromatic), 1469 (C=C stretching of aromatic ring), and 654 (Ru–C), and 577...
The IR spectra of (a) compound 1 and (b) ruthenium(II) complex 2.

The complexation of compound 1 to the ruthenium(II) metal center can be further supported by the UV–Vis data as shown in Figure 4. In the case of compound 1, two absorption bands were observed at 273 and 372 nm, which are assigned to the transitions of benzene rings and aromatic azine group, respectively. After the complexation, both the absorption bands undergo significant bathochromic shifts to 293 and 372 nm, respectively. The confirmation of these shifts of two absorption bands have proven the complexation of 1 with ruthenium(II) metal center via the nitrogen atom from in the C=N and C= C bond of the aliphatic C=C moity.

The singlet at 29.88 ppm reveals that the two PPh₃ units are magnetically equivalent in the ruthenium(II) complex. There are three possible structures based on this singlet. In the first case, the two PPh₃ units are located at the axial positions of an octahedron and are-chelate trans to each other (Figure 2(a)). In the other two cases, they are located on the equatorial plane, which is only trans to one of the C atoms from in the C=C bond (Figure 2(b)) or the N atom from in the N=C=C bond (Figure 2(c)).

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 Figure 4(a). Lastly, The other another pair of doublets at 49.80 and 47.36 ppm with a coupling constant of 38 Hz is assigned to the trans isomer of ruthenium(II).
complex shown in (Figure 25(b)). It is evident that the difference in the coupling constants between the ruthenium(II) complexes shown in Figures 3(a) and 3(b) is due to the positions of the PPh₃ ligands. The doublet with a smaller coupling constant (trans, cis: 21 Hz) was assigned to the cis isomer because both the PPh₃ ligands are in the equatorial plane. The two absorption bands shift accordingly after binding to ruthenium(II) metal centre. For C=N stretching band, it shifted from 1627 cm⁻¹ in compound 1 to 1661 cm⁻¹ in ruthenium complex [9–10] whereas for C=C stretching, the IR band appears at 1601 cm⁻¹ in compound 1 but it is not clearly shown in the complex because the IR bands of C=C bands for aliphatic and aromatic were merging into one broad IR band centred at 1576 cm⁻¹. Nevertheless, two additional IR peaks are present in the fingerprint region at 572 and 654 cm⁻¹ indicating the formation of respective Ru-N and Ru-C bands [11].

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

The complexation of compound 1 to ruthenium(II) metal centre can be further supported by the UV--Vis data as shown in Figure 5. For compound 1, two absorption bands were observed at 273 and 322 nm which are assigned to transition of the benzene ring and transition of the imine group [12], respectively. After the complexation, both absorption bands shift to 321 and 382 nm, respectively. Significant shift of these two absorption bands have proven compound 1 was successfully bound to ruthenium(II) metal centre via the nitrogen atom from C=N group and carbon atom from C=C double bond to ruthenium(II) complex in the C=C CC=N moiety. The bathochromic shift of these two absorption bands was due to the backbonding of electrons from Ru to the antibonding orbitals of C=C CC=N moiety in compound 1. This, in turn, has weakened the bond in C=C CC=N [12].

Figure 5: UV--Vis spectra of compound 1 (a) and ruthenium(II) complex (b).

In addition, the data from IR and UV--Vis revealed the successful binding of compound 1 has bound to the ruthenium(II) metal centre was confirmed from the IR and UV--Vis spectral data.

4. Conclusion

The ¹H NMR spectra revealed the evidence from ¹H NMR spectrum has shown the presence of three isomers of the bis(diphenylamine)-1,4-azabutadiene-bis(triphenylphosphine)ruthenium(II) complex in the 1:1:1 ratio at [11,12]. Two of the three isomers are those shown in Fig. 5: i.e., one cis and one trans isomer, while the third isomer could be any one of those shown in Fig. 4. In addition, the data from IR and UV--Vis revealed that compound 1 has bound to ruthenium(II) metal centre.

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Highlight 15

Three isomers were detected for a phosphine-bearing Ru complex using 1H NMR.
Formation of Ru-N and Ru-C bonds were confirmed by FTIR spectroscopy.
At least one cis isomer and one trans isomer of the complex were formed.

References

Highlights
- Three isomers were detected for a phosphine-bearing Ru complex using ¹H NMR.
- Formation of Ru-N and Ru-C bonds were confirmed by FTIR spectroscopy.
- At least one cis isomer and one trans isomer of the complex were formed.