The enigma of persistent hypertriglyceridemia: A Case Report

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Abstract

A patient with a history of Mandibular hypoplasia, Deafness, Progeroid Features Associated Lipodystrophy Syndrome (MDPL), a familial lipodystrophy presented with hypertriglyceridemia induced pancreatitis with triglycerides in the 3000s. This lipodystrophy occurs due to a mutation in the POLD1 gene (DNA polymerase delta 1).

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Introduction

Hypertriglyceridemia is defined as a serum triglyceride (TG) level >150 mg/dL (1.7 mmol/L).[1]It is commonly detected as a part of routine blood work which includes a fasting lipid panel to assess for cardiovascular risks. It is categorized into three groups based on the triglyceride levels-

- Normal: <150 mg/dL (1.7 mmol/L)
- Moderate hypertriglyceridemia: 150 to 885 mg/dL (1.7 to 10 mmol/L)
- Severe hypertriglyceridemia: >885 mg/dL ([?]10 mmol/L)

Atherosclerotic cardiovascular diseases like myocardial infarction and cerebrovascular accidents are more common in patients with elevated fasting plasma TG levels[2].1 to 10 percent of acute pancreatitis cases are caused by hypertriglyceridemia[3].

A less common cause of hypertriglyceridemia is Lipodystrophy, which involves fat loss in a generalized or partial pattern and is often associated with hypertriglyceridemia, diabetes mellitus, and hepatic steatosis. Lipodystrophies are classified as either genetic or acquired[4]. The acquired forms are usually caused by various infections, autoimmune diseases, and drugs such as protease inhibitors and reverse transcriptase inhibitors. Genetic lipodystrophies areelucidated in the discussion section of the report.

Case presentation

This report highlights the decision-making involved in managing a patient who had refractory hypertriglyceridemia, followed by a review of genetic lipodystrophies. The patient is a 43-year-old female with a past medical/surgical history significant for diabetes mellitus, hypertriglyceridemia, hypertension, fibromyalgia, GERD, Sjogren's syndrome, Rheumatoid arthritis,irritable bowel syndrome, and cholecystectomy. Her home medications are listed in Table 1.She presented to the hospital for persistent abdominal, flank and chest pain refractory to pain management with acetaminophen and ibuprofen at home. This pain started after she was setting decoration for the holidays. She denied anyassociated nausea, vomiting, fevers, chills, recent constipation, diarrhea, shortness of breath, cough, palpitations, or dysuria.

Metformin 1000 mg twice daily
Glipizide 10 mg twice daily
Pioglitazone 40 mg twice daily
Fenofibrate 145 mg once daily
Atorvastatin 40 mg once daily
Lisinopril-HCTZ 10-12.5mg once daily
Methocarbamol 500mg twice daily
Insulin Lantus 12 U once daily
Humira 40mg once weekly
Leflunomide 10 mg once daily
Tramadol 50 mg once daily
Pilocarpine 5 mg once daily
Dicyclomine 20 mg once daily
Lansoprazole 30 mg once Q Mon, Wed, Fri & Sat
Fish oil

Table 1. Patient's list of home medications before admission

She denied any alcohol or recreational drug use. She quit smoking a few years back. Her mother had a history of myocardial infarction, diabetes mellitus, hypertension, and Rheumatoid arthritis. Her family is originally from Mexico, and one of her brothers and her two cousins have elevated triglycerides.

Physical examination was significant for tenderness in the epigastric and bilateral costovertebral area. Her abdomen had disproportionatelyincreased fat deposition while her arms and legs were skinny (due to lipodystrophy).

Her blood pressure was 125/89 mm Hg, heart rate was 140 bpm, temperaturewas 36.3 C, and respiratory rate was 17 breaths/ minute.

The differentials based on her symptoms and physical examination included-

- Acute Coronary Syndrome
- Aortic Dissection
- Pulmonary Embolism
- Gastroesophageal Disorder
- Urinary Tract Infection
- Acute Pancreatitis
- Musculoskeletal Strain

Her CBC showed a WBC count of 11.2 K/mm3 with neutrophilic predominance (reference range 4-11 K/mm3), Hb of 13.4 g/dL (reference range 12-16 mg/dL), Hematocrit of 40% (reference range 35-48%) and a platelet count of 258 K/mm3 (reference range 130-450 K/mm3). Her urinalysis revealed the presence of blood and 3-10 RBCs/hpf. Other pertinent lab results are shown in Table2.

Variable	Value	Reference range in hospital
BUN	9 mg/dL	8-25 mg/dL
Creatinine	0.35 mg/dL	0.6-1.4 mg/dL
Sodium	127 mmol/L	134-147 mmol/L
Potassium	4.6 mmol/L	3.5-5.3mmol/L
Chloride	89 mmol/L	95-108 mmol/L
Bicarbonate	19 mmol/L	19-31 mmol/L
Glucose	271 mg/dL	70-106 mg/dL
Calcium	9.3 mg/dL	8.8-10.4 mg/dL
Total protein	7.5 g/dL	6-8 g/dL
Albumin	3.8 g/dL	0.4-5.1 g/dL
Total bilirubin	0.5 mg/dL	0.2-1.3 mg/dL
AST	40 U/L	10-41 U/L
ALT	20 U/L	5-46 U/L
ALP	30 U/L	37-127 U/L
Troponin	8 ng/L	<11 ng/L
Lactic Acid	2.1 mmol/L	0.5-2.2 mmol/L
D-dimer	537	<500
Total cholesterol	452 mg/dL	<199 mg/dL
HDL	8 mg/dL	>50mg/dL
Triglycerides	**3,154 mg/dL**	<149 mg/dL
Lipase	172 U/L	16-63 U/L

Table 2. Lab results on admission

In the Emergency Department, she received 1L of Normal saline and 4mg of IV morphine for pain control. Her chest X-ray did not show any acute cardiopulmonary process. Her low troponin and absence of EKG changes rendered Acute coronary syndrome unlikely. Her urinalysis was negative for an infection. A CT Angiogram of the chest and abdomen was performed: This ruled out any aortic pathology and PE and was positive foracute pancreatitis.The patient met all three criteriaof acute pancreatitis with elevated lipase levels, epigastric pain and imaging findings of pancreatitis with elevated triglycerides confirming the diagnosis of acute pancreatitis secondary to hypertriglyceridemia. She was admitted for further management. She was kept nil per oral, and we managed her pain with oxycodone and morphine. She was able to consume a clear liquid diet a day after her presentation and was easily transitioned to a regular diet.

We started an insulin drip at a rate of 5 units/ hour intending to lower her triglycerides below 500mg/dL. Dextrose 5% half-normal saline with 40 mEq/L of Potassium was initiated at 250 ml/hr;insulin and glucose checks every 1 hour were requested for monitoring. Her electrolytes and triglycerides were monitored every four hours. After one day of being on an infusion insulin, she was transitioned tosubcutaneous glargine insulin 20 units daily.

However,8 hoursafter transitioning to subcutaneous insulin, hertriglycerides started to rise again requiring re-initiation of IV insulinand the need for an endocrinology consult. They recommended starting 20 units of subcutaneous glargine with 8 units of lispro. In addition, we restarted her fenofibrate 160 mg daily and increased her statin to 80 mg daily. Her triglycerides eventually dropped below 1000in a daybut fluctuated at levels over 500. Subsequently, she was discharged on glargine, Fenofibrate, atorvastatin, and fish oil with her triglyceride levels in the 500s with close outpatient endocrinology follow up. A further decline in triglycerides was not pursued due to concerns for hypoglycemia and reduced incidence of hypertriglyceridemia induced pancreatitis at levels in the 500s.

Her Leflunomide for Rheumatoid, Pilocarpine for Sjogren, PPI for GERDand Dicyclomine for Irritable Bowel Syndrome were resumed at discharge.

Discussion

The patientpresented to our facility for the first time in 2016 for lipodystrophy with a history of diabetes mellitus and menstrual cramps. She was on oral contraceptives. She was noted to have fat maldistribution with a protuberant abdomen and skinny legs and arms. Her mandible was hypoplastic, and she also had sensorineural hearing loss. POLD 1 (DNA Polymerase Delta 1) mutation was suspected given a positive family history: Her mother had lipodystrophy and died at age 68 due to a myocardial infarction but no information about her father, a visiting Austrian.Twoout of her four maternal brothers have lipodystrophy and one also has crowded teeth. One brother also has 2 children with lipodystrophy with no genetic evaluation. Her grandmother had similar features and died at age of 80. She also has two maternal uncles with lipodystrophy.She has a mixed European and Native Indian ancestry with no Jewish heritage and consanguinity. Her cousin and nephew also had a history of Mandibular Hypoplasia, Deafness, progeroid features, and lipodystrophy syndrome (MDLP).

She was tested for POLD1 gene mutation, which revealed the presence of a variant of uncertain significance (UVUS), c.1519C>T (p.Arg507Cys) in POLD1, prompting further evaluation of her condition. Researchers, particularly a metabolic disease expert and a lipidologist interested in her case, were contacted [what was their contribution?]. This sequence change replaces arginine with cysteine at codon 507 of the POLD1 protein. The arginine residue is highly conserved, and there is a sizeable physiochemical difference between arginine and cysteine. This variant was not found to be in the population databases at that time.

Lipodystrophies include a heterogeneous group of disorders that share certain features, particularly fat loss in a generalized or partial pattern associated with hypertriglyceridemia, diabetes mellitus, and hepatic steatosis. Lipodystrophies are classified as either genetic or acquired. Acquired forms are usually caused due to various infections, autoimmune diseases, and drugs such as protease inhibitors and reverse transcriptase inhibitors. There is a growing consensus amongst the medical community to elucidate the genetic causes of lipodystrophies. Research in the area is yielding results, but a lot remains to be comprehended. A brief overview of currently known genetic lipodystrophies is presented in the discussion.

According to a literature review, about 1000 patients have been found to have genetic lipodystrophies[5]. Congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPL) are two important forms. CGL presents withovert features of lipodystrophy and can be diagnosed at birth. However, FPL is commonly misdiagnosed as metabolic syndrome in adult life due to overlapping common clinical features noticed in the two conditions.

Mandibular hypoplasia, Deafness, Progeroid Features Associated Lipodystrophy Syndrome (MDPL)

MDPL is an autosomal dominant systemic disorder with about 22 patients reported worldwide till 2018. Classical phenotypic features consist of loss of subcutaneous fat, small mandible resulting in lower teeth overcrowding, premature aging, sensorineural hearing loss, prominent eyes, and a beaked nose. Despite having a low BMI, metabolic abnormalities like diabetes mellitus and hypertriglyceridemia are commonly observed. Males display cryptorchidism and hypogonadism, with certain females presenting with menstrual irregularities like amenorrhea and dysmenorrhea.

Mutations in the Polymerase delta gene (POLD 1) gene that performs DNA synthesis in the lagging strand during DNA replication is responsible for MDPL presentation[6].Heterozygous de novo mutations in the POLD 1 gene with most cases involving single codon deletion (p.S605del) lead to the decreased catalytic activity of POLD 1 enzyme with a partially altered proofreading activity, making it the deletion hot spot for MDPL. Some cases have been reported to have a missense mutation (p.R507C) replacing arginine with cytosine.

Mandibuloacral hypoplasia associated Lipodystrophy (MAD)

MAD is a rare autosomal recessive systemic disorder that presents with lipodystrophy, growth retardation, skeletal abnormalities, mandibular hypoplasia, and mottled cutaneous pigmentation. The absence of diabetes mellitus, helping to differentiate between MDPL and MAD[7].

Werner Syndrome

Werner Syndrome (Adult progeria), an autosomal recessive disorder, is characterized by premature aging with other age-related diseases, short stature, and bilateral cataracts[8].

Proteasome-associated Autoinflammatory Syndromes (PRAAS)

PRAAS is an autosomal recessive disorder that presents with partial lipodystrophy, plaques on the face and extremities, basal ganglia calcifications, and joint contractures[9].

Other entities that fall into the category of Molecular Lipodystrophies include

- Short stature, Hyperextensibility of Joints and/or Inguinal hernia, Ocular Depression, Reiger Anomaly and Teething Delay Syndrome (SHORT)

- Neonatal Progeroid Syndrome/Wiedemann-Rautenstrauch Syndrome (WR)

Marfanoid-Progeroid-Lipodystrophy Syndrome (MPL)

Conclusion

Hypertriglyceridemia can be associated with acquired and congenital lipodystrophies.Such cases present a unique challenge in managing elevated triglyceride levels. . One of the types of congenital lipodystrophy syndromes is Mandibular hypoplasia, Deafness, Progeroid Features Associated Lipodystrophy Syndrome (MDPL). This syndrome is caused by a mutation in the POLD 1 gene which can alter its proofreading activity. Loss of subcutaneous fat, small mandible resulting in lower teeth overcrowding, premature aging, sensorineural hearing loss, prominent eyes, and a beaked nose are often seen. Metabolic abnormalities like diabetes mellitus and hypertriglyceridemia are commonly observed key features.Identifying this mutation and thus diagnosing this syndrome as the cause of hypertriglyceridemiacanhelp in making appropriate lifestyledecisions. For certain genetic conditions, it can also allow for more regular check-ups for monitoring for thedevelopment of future symptoms that can be expected in those syndromes.

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Conflict of Interest

None

Author Contribution

1. Armaan Dhaliwal – Collected data, did research and wrote manuscript
2. Soumiya Ravi – Did research and wrote manuscript
3. Kanwal Bains – Did research and wrote manuscript
4. Anil Kumar Potharaju – Involved in correction of the manuscript
5. Tasneem Shah – Involved in correction of the manuscript

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