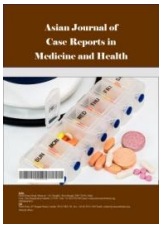

Asian Journal of Case Reports in Medicine and Health

5(2): 7-13, 2021; Article no.AJCRMH.66716

Case Report of a Patient with Mauriac Syndrome

Suprianto Suryono[1*], Muhammad Umer Malik[2], Chee Kwang Yung[2], Edwin Lim Chyi Chyuan[3] and Pg Adli Pg Metussin[4]

[1]Raja Isteri Pengiran Anak Saleha Hospital, Brunei.
[2]Endocrinology RIPAS Hospital, Brunei.
[3]Pathology RIPAS Hospital, Brunei.
[4]Gastroenterology RIPAS Hospital, Brunei.

Authors' contributions

This work was carried out in collaboration among all authors. Author SS collected data and wrote the first draft of the manuscript. Author MUM, proofread the manuscript. Author CKY did the final editing of the manuscript. Authors ELCC and PAPM contributed with their specialty consultations and investigations. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Professor. Ayhan Goktepe, Selçuk University, Turkey.
Reviewers:
(1) Mihaela Victoria Vlaiculescu, Carol Davila University of Medicine and Pharmacy, Romania.
(2) Wallace Rodrigues de Holanda Miranda, Federal University of Piauí, Brazil.
Complete Peer review History: http://www.sdiarticle4.com/review-history/66716

Case Study

Received 20 January 2021
Accepted 24 March 2021
Published 30 March 2021

ABSTRACT

We would like to present an interesting and rare case of a 16-year boy, with the background of Type 1 diabetes since the age of 11 years who presented with Diabetic Ketoacidosis (DKA). He had multiple admissions with DKA in the preceding two years and his liver function tests were found to be deranged during the last two presentations. This was further evaluated through various investigations and a diagnosis of Mauriac syndrome was made.

Keywords: Diabetic ketoacidosis; chronic disorder; type 1 diabetes child; mauriac syndrome.

1. INTRODUCTION

Diabetes mellitus is a chronic disorder characterized by hyperglycaemia due to insulin deficiency and/or insulin resistance. The prevalence of people with Type 1 Diabetes amounts to 9.5% of all the cases of diabetes worldwide [1]. Poor metabolic control for patients

**Corresponding author: E-mail: supri.suryono@gmail.com;*

with diabetes is strongly associated with increased risk of micro- and macro- vascular complications. There is a much rarer complication associated called Mauriac Syndrome that is characterized by hepatomegaly, growth failure, delayed puberty, and cushingoid features.

The main stay of treatment in Maurice syndrome is to intensify the Insulin regime to improve glycemic control, which can result in a complete remission of clinical and laboratory abnormalities. Glycogenic hepatopathy can also resolve as quickly as it develops within days to weeks with good glycemic control [2].

2. CASE PRESENTATION

This is a 16-year old boy with known Type 1 Diabetes(T1DM) admitted on 19/10/2019 in an emergency with one-day history of four episodes of vomiting and single episode of watery stool in Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, Brunei Darussalam. There was no history of fever or any focal constitutional symptom prior to the presentation. His random blood capillary blood glucose was 33.2mmol/L with a capillary ketone of 3.1 mmol/L. The venous blood gas showed metabolic acidosis with a pH of 7.05, bicarbonate of 6.4 mmol/L and base excess of -22.4 . The chest x-ray did not show any consolidation or effusion and his electrocardiogram showed sinus tachycardia at a rate of 112 beats per minute. A diagnosis of moderate diabetic ketoacidosis was made and he was started on intravenous fluid resuscitation along with intravenous insulin infusion. Empirical antibiotic with intravenous co-amoxiclav was also started. He was referred to the Critical Care Unit and then transferred to the Intensive Care Unit (ICU) for further management directly from the emergency department. The patient was subsequently transferred out from the ICU to the general ward upon resolution of the DKA.

Further history was obtained from the patient which did not suggest any obvious source infection. The blood cultures were negative after five days and his antibiotic was oralised to complete the duration. There was no reported history of substance abuse. In terms of his education he has been underperforming in school.

He was first diagnosed as Type 1 DM in 2014 at the age of 11 years when he first presented in pediatric units with Diabetic ketoacidosis. His fasting C-peptide was low with a reading of 37 pmol/l (370 to 1470 pmol/l) and his insulin antibodies for Anti-Glutamic Acid Decarboxylase and Anti-IA2 antibodies were negative at the time of diagnosis. He has a chronic history poor glycaemic control due to poor compliance to dietary advice as evident by his persistently elevated glycated haemoglobin (please refer to Table 1. This poor metabolic control is further compounded by his social background with poor family support and low socio-economic circumstances. His diet was unrestricted and admitted to regularly consuming sweets, cakes and carbonated drinks. Prior to admission he was on insulin aspart 8U/kg (1.1units/kg) prebreakfast, 10U/kg (1.1units/kg) pre-lunch, 8U/kg (1.1units/kg) pre-dinner and insulin glargine 30U/kg (1.1units/kg) once daily.

Clinically he was proportionately short with measured height of 135 cm (5^{th} centile) and weighed at 45 kg (75^{th} centile). He had a puffy cheek with increased abdominal girth. There were no other stigmata of Cushing Syndrome present. The abdominal examination showed a smooth, non-tender hepatomegaly with lipohypertrophic Injection sites. There was no axillary hair with scanty hair growth in around the pubic area. His testicular examination showed Tanner stage of 2 suggestive of pubertal delay. The rest of respiratory, cardiovascular and neurologic examination were unremarkable. His chronic disease followed up on the outpatient setting which included a multi disciplinary team which involved the Endocrinologist, Diabetic Nurse educator, dietician, and yearly retinal eye screening in the Ophthalmology department which he defaulted.

In view of the hepatomegaly finding, the liver function test (LFT) was ordered. This showed a hepatitis picture with predominant elevation in the transaminitis a shown in Table 2.

Following a consult with a gastroenterologist, it was recommended to exclude other differential diagnosis such as non-alcoholic fatty liver disease(NAFLD), autoimmune hepatitis, infection and other metabolic disorders as shown in Table 3.

With the results of these investigations were in normal limits, the cause of the patient's hepatomegaly excluded disorders such as Thyroid disease, Alpha-1 Antitrypsin deficiency, Haemachomatosis, Wilsons disease and Coeliac Disease. His basal cortisol was also within normal limits.

A panel to screen for viral infection as a cause of the derangement of liver markers showed negative for Hepatitis A, B, C and Human Immunodeficiency Virus (HIV). The cytomegalovirus virus (CMV) positive IgA and IgG and negative IgM indicates latent infection. With regards to the Ebstein Barr Virus (EBV) the positive EBV IgM and IgG reflects on activation of latent infection. The Equivocal results of the Herpes Simplex Virus (HSV) may indicate current of past HSV infection.

As the autoantibodies screening yielded negative, pathologies related to autoimmune hepatitis was ruled out as seen in Table 5. Subclasses of immunoglobulin showed in Table 6 were in normal limits. IgG4 – related disease is a systemic disease which can affect and infiltrate the hepatobiliary system. Normal limits of IgG4 excludes IgG4 – related autoimmune hepatitis (AIH) and IgG4 hepatopathy [3].

In view of the hepatomegaly and deranged liver function tests, an ultrasound of his abdomen was done which reported an enlarged liver with a smooth surface and slightly coarse parenchymal echogenicity with no suspicious focal lesion. Intrahepatic bile ducts were not dilated. The portal vein diameter was normal with no thrombosis. There was no hepatic vein thrombosis noted. We proceeded next with a computed tomography (CT) scan of his abdomen that showed a gross enlarged liver with the right lobe measuring 22.4cm. The gallbladder was normal and the pancreas appeared atrophic in keeping with a T1DM patient. Please refer to Fig. 3 and 4 below.

Table 1. Shows the glycated haemoglobin(HbA1c) results over the preceding two years

Date	05/06/18	19/09/18	20/10/18	12/01/19	06/07/19	09/09/20
HbA1c (%)	3.1	1 2.2	12.1	14.0	14.9	14.0

Table 2. Liver Function Test (LFT) Trend in 2019

Date	Bilirubin(5-30 umol/L)	ALT(1-54 nol/L)	ALP(30-110 umol/L)	GGT(12-64 umol/L)	Albumin(35-50 umol/L)	Protein(60-83 g/L)
19/10/19	17.7	785	215	462	48	82
05/09/19	5.9	55	152	107	53	95
05/07/19	11	37	146	97	56	99

Table 3. Other investigations to rule out liver pathologies

Other Investigations	Results
TFT (TSH)	1.03 (0.51-4.30mIU/L)
Alpha-1 Antitrypsin	1.0 (0.9-2.0 g/l)
Ferritin	204 (30-400ug/l)
Serum Ceruloplasmin	2 (0.2-0.6g/l)
Anti-tissue transglutaminase antibodies	Negative

Table 4. Viral Panel

Virology	Hepatitis A	Hepatitis B	Hepatitis C	HSV IgM	HIV
Results	Negative	Negative	Negative	Equivocal	Negative
Virology	EBV IgM	EBV IgG	CMV IgM	CMV IgA	CMV IgG
Results	Positive	Negative	Negative	Positive	Positive

Table 5. Immune antibodies profile

Immune Markers	Antinuclear Antibodies	Antimitochondrial Antibodies	Anti-Smooth Muscle Antib-odies	Anti parietal Cell Antibodies
Results	Negative	Negative	Negative	Negative

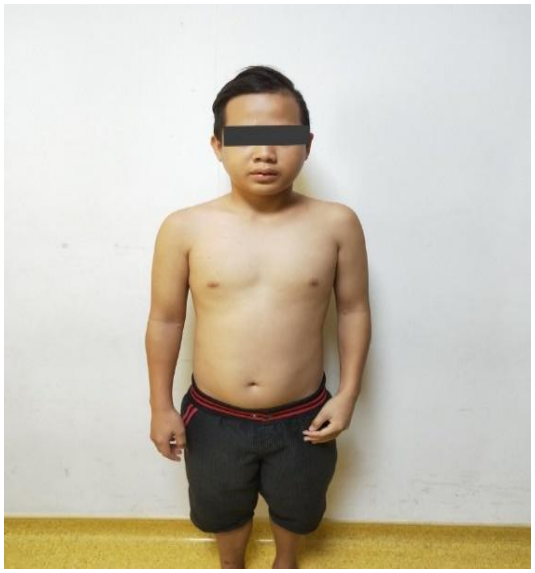

Fig. 1. Morphological syndrome (front view)

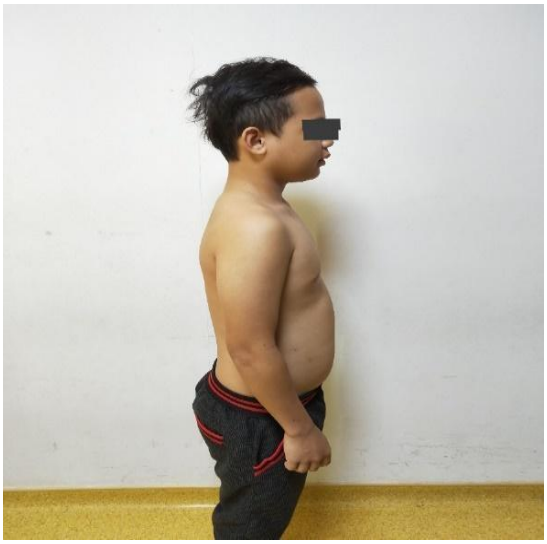

Fig. 2. Morphological syndrome (side view)

Table 6. Immunoglobulin profile

Immunoglobulin	IgA	IgG	IgM	IgE	IgG4
Results	1.7 (0.63-4.84) g/L	8.82 (5.40-18.22) g/L	0.64 (0.22-2.4) kU/L	1763 (0-100) kU/L	55.7(0.3-111.0 mg/dL

In view of the radiological finding of features suggestive of NAFLD and, persistent raised transaminases, ultrasound guided core biopsy was advised to help ascertain the underlying cause of his liver disease. He and his mother were explained on the indications, nature of the procedure including complications as part of consent. They both consented to the procedure and a 15mm sample was excised assessing 3 portal tracts with no immediate complication. The biopsy sample was sent off to the pathology laboratory for formal reporting.

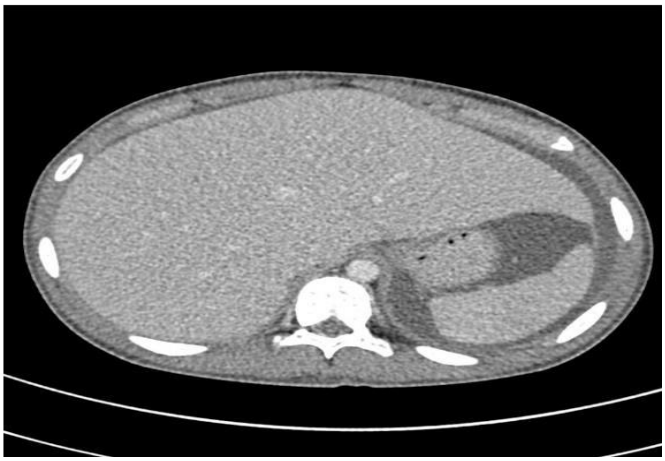

Fig. 3. CT Abdomen and pelvis scan

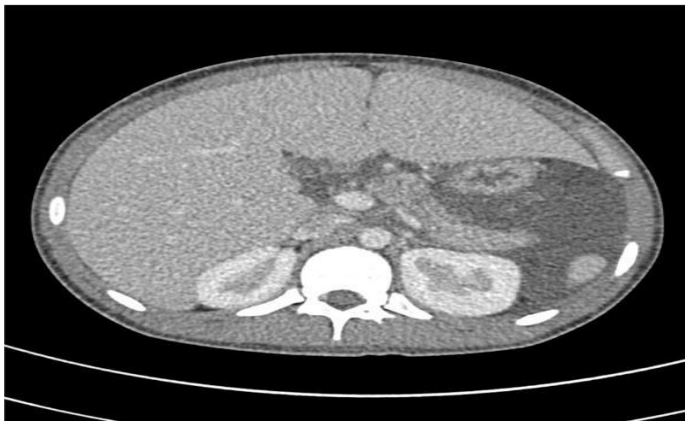

Fig. 4. CT Abdomen and Pelvis Scan shows a shrunken pancreas (arrow*)*

The report showed hepatocytes diffusely swollen, pale and occasionally vacuolated with centrally placed nuclei and are arranged in a uniform mosaic pattern Figs 5 and 6. There was an abundant of glycogen accumulation within the cytoplasm as indicated by positive Periodic acid Schiff (PAS). stain Fig. 5 and negative Periodic acid Schiff diastase(PASD) stain Fig. 6. This gave the hepatocytes a plant cell like appearance. The sinusoids are compressed and the portal tracts appear unremarkable with no bile duct pathology and no significant portal inflammation or fibrosis. There was minimal pericellular fibrosis noted. There was no evidence of Alpha 1 antitrypsin (A1AT) globule or Hemosiderin deposition.

Hence a definitive diagnosis of Mauriac syndrome was made based on the histology report and negative work up for the other potential differential causes.

3. DISCUSSION

Mauriac syndrome is a rare condition associated predominantly with poorly controlled Type 1 Diabetes Mellitus and rarely in T2DM resulting in the development of glycogen hepatopathy with growth failure, delayed puberty, and cushingoid features. The hallmark of the glycogenic hepatopathy is severe fluctuation in levels of glucose and administration of supraphysiologic levels of insulin to control the hyperglycemia. Hepatomegaly in Maurice syndrome can develop within days to weeks and can improve rapidly once the hyperglycemia is controlled [2]. GH was first reported after short-acting insulins became available for the treatment of DM. Initially, when short acting insulins were used for the treatment of DM, large doses of insulin were required to control hyperglycemia, causing consequent hypoglycemia. This vicious cycle of excessive doses of short-acting insulin and subsequent

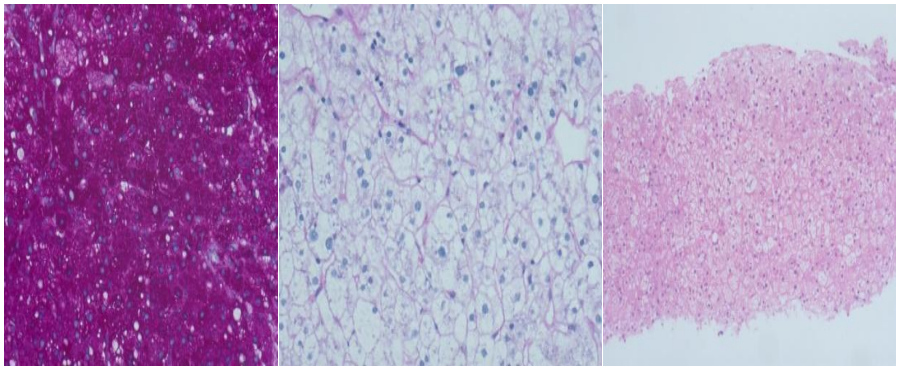

Fig. 5. PAS stain **Fig. 6. PASD stain** **Fig. 7. H&E stain**

administration of glucose to counteract the resulting hypoglycemia could have led to the continued accumulation of glycogen in the liver, a proposed mechanism by various authors [4]. These findings are infrequently observed today due to widespread use of long-acting insulin and possibly the decreased frequency of hypoglycemic events in this patient cohort [2].

The actual incidence and prevalence of GH are not known. 62% of the reported cases are female with most cases occurring in adolescence. Based on published reports in medical literature, approximately 98% of GH cases were reported in T1DM, while T2DM cause the remaining 2%. The incidence of this syndrome has decreased significantly with the introduction of long-acting insulin, continuous Insulin pump and better control of diabetes [5,6].

This syndrome is thought to be secondary to inadequate glucose utilization in tissues, decreased insulin-like growth factor-1 (IGF-1) and growth hormone levels or resistant/defective hormone receptors; However, précised etiology is unknown [7]. The mechanism of delayed growth could be related to the low levels of IGF-1 and growth hormones. Low sex hormones could also play a part in the reduced action of insulin and nutrition [8]. In patients with a classic presentation of Mauriac syndrome, intensifying Insulin regime to improve glycemic control can result in a complete remission of clinical and laboratory abnormalities [6]. Physiologically, the liver takes up glucose and either utilize it for fuel or stores as glycogen. Thus, hepatic glycogen level is maintained by the balance between glycogenosis and glycogenolysis. High glucose levels cause an influx of glucose into the hepatocytes *via* facilitated diffusion through the glucose transporter 2 (GLUT2), independent of insulin. Once the glucose is present within the hepatocytes, the enzyme glucokinase irreversibly phosphorylates glucose to glucose-6-phosphate, trapping it within the hepatocytes. Subsequent treatment of hyperglycemia with the high dose of insulin enhances the further conversion of trapped glucose to polymerize into glycogen.

Another proposed theory suggests the excess of hormones like adrenaline, cortisol, or growth hormones released due to hypoglycemia, could synergistically act and release large quantities of non-esterified fatty acids from adipose tissue. This high concentration of free fatty acids inhibits glucose oxidation in muscles, and they may have similar effects on liver promoting excess storage of glycogen [9].

A study by MacDonald and colleagues of an adolescent boy with Mauriac syndrome identified a mutation in PHKG2, the catalytic subunit of glycogen phosphorylase kinase [10]. Expression of the mutant PHKG2 in a human liver cell line inhibited the enzyme activity of the phosphokinase complex and increased glycogen levels leading to glycogen storage diseases [10].

Glycogen hepatopathy is potentially a reversible condition through optimization of glycemic control. This also provides a role for reversing pubertal delay and its other clinical features [11,12-14].

with chronic poor glycaemic control and recurrent DKA who present with abnormal liver function tests and hepatomegaly associated with growth and pubertal delay.

4. CONCLUSION

This rare case highlights the importance to consider Mauriac Syndrome in T1DM patients

CONSENT

Patient and mother consents for publication of this case report and accompanying image and photos were taken.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mobasseri M, Shirmohammadi M, Amiri T, Vahed N, Hosseini Fard H, Ghojazadeh M. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. Health Promotion Perspectives. 2020;10(2):98-115.
2. Sherigar JM, Castro J, Yin YM, Guss D, Mohanty SR. Glycogenic hepatopathy: a narrative review World J Hepatol. 2018; 10(2):172-185
3. Ishizu Y, Zen Y, Harada K, Umemura T, Nakanuma Y. Histopathology of IgG4-Related Autoimmune Hepatitis and IgG4-Related Hepatopathy in IgG4-Related Disease. Seminars in Liver Disease. 2016; 36(03):229-241.
4. Murata F, Horie I, Ando T, Isomoto E, Hayashi H, Akazawa S, et al. A case of glycogenic hepatopathy developed in a patient with new-onset fulminant type 1 diabetes: the role of image modalities in diagnosing hepaticglycogen deposition including gradient-dual-echo MRI. Endocr J. 2012;59:669-676.
[PMID: 22673296]
5. Johnson SR, Cooper MN, Jones TW, et al. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case–control study. Diabetologia. 2013;56: 2392–2400.
6. Kim MS, Quintos JB. Mauriac syndrome: growth failure and type 1 diabetes mellitus. Pediatr Endocrinol Rev. 2008;5 (4):989–993.
7. Progressive retinopathy with improved control in diabetic dwarfism (Mauriac's syndrome). Daneman D, Drash AL, Lobes LA, Becker DJ, Baker LM, Travis LB Diabetes Care. 1981;4(3):360-5.
8. Mauras N, Merimee T, Rogol AD. Function of the growth hormone-insulin-like growth factor 1 axis in the profoundly growth-retarded diabetic child: evidence for detective target organ responsiveness in the Mauriac syndrome. Metabolism. 1991;40:1106–1111.
9. Berman MC. Hepatic glycogen storage during uncontrolled diabetes mellitus. A case report. S Afr Med J. 1973;47:184-186. [PMID: 4684248].
10. MacDonald MJ, Hasan NM, Ansari IH, Longacre MJ, Kendrick MA, Stoker SW. Discovery of a genetic metabolic cause for Mauriac syndrome in type 1 diabetes. Diabetes. 2016;65:2051-2059
PMID: 27207549
DOI: 10.2337/db16-0099
11. Topaloglu O, Demiral S, Demir B, Akaren D. Mauriac Syndrome: Case Report and Review of the Literature. The Turkish Journal of Endocrinology and Metabolism. 2017;21(4):131–135.
12. Mauriac P. Grosventre, hepatomegalie, troubles de la croissance chez les enfants diabetques, traits depuisplusieursanbnees par l'insuline. Gaz Hebd Sci Med Bordeux. 1930;51:402.
13. Mahesh S, Karp RJ, Castells S, Quintos JB. Mauriac syndrome in a 3-year-old boy. Endocr Pracr. 2007;13:63–6.
14. Giordano S, Martocchia A, Toussan L, Stefanelli M, Pastore F, Devito A, et al. Diagnosis of hepatic glycogenosis in poorly controlled type 1 diabetes mellitus. World J Diabetes. 2014;5:882–8.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/66716