Case report

Autoimmune hepatitis and acquired partial lipodystrophy

Christopher Bakewell ,[1] Kavinda Dayasiri,[2] Rachel M Brown,[3] Astor Rodrigues,[1] Rachel Williams,[4] Geetha Anand,[2] Girish L Gupte[5]

[1]Paediatric Gastroenterology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[2]Department of Paediatrics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[3]Department of Cellular Pathology, Queen Elizabeth Hospital Birmingham, Birmingham, UK
[4]National Severe Insulin Service, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[5]Liver Unit (including Small Bowel Transplantation), Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

Correspondence to
Dr Geetha Anand, Department of Paediatrics, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; geetha.anand@ouh.nhs.uk

Received 24 February 2021
Revised 22 April 2021
Accepted 1 May 2021
Published Online First 14 May 2021

To cite: Bakewell C, Dayasiri K, Brown RM, *et al*. *Frontline Gastroenterology* 2022;**13**:175–177.

ABSTRACT

The lipodystrophies are an extremely rare group of metabolic conditions which are categorised based on their pathogenesis and phenotype. While primarily known for the striking loss of subcutaneous adipose tissue which they induce, they may also be associated with significant liver injury. In most cases, this results from the secondary deposition of lipid within hepatic parenchyma and is seen predominantly in generalised lipodystrophy. More rarely, patients may develop autoimmune hepatitis. We report a rare case of a 17-month-old boy who developed features of acquired partial lipodystrophy in association with anti-LKM1-positive autoimmune hepatitis following initial presentation with a Henoch-Schönlein purpura-like illness. We describe his challenging path to diagnosis and discuss his ongoing management in an effort to further our understanding of this rare but significant association. This report highlights the need for close clinical observation and a high index of suspicion for recognising early features of lipodystrophy.

BACKGROUND

The lipodystrophies are a rare and heterogeneous group of disorders which have an estimated prevalence of 1.3–4.7 cases/million.[1] Best known for the striking loss of subcutaneous adipose tissue they induce, these conditions can also cause an array of endocrine–metabolic disturbances secondary to leptin deficiency/resistance.[2] While their pathogenesis is not fully understood, they can be subcategorised based on their onset and phenotypical appearance into four groups: congenital generalised lipodystrophy, congenital partial lipodystrophy, acquired generalised lipodystrophy and acquired partial lipodystrophy (APL). This division is clinically important, not least because the disease course is highly variable between groups.

Liver disease represents a significant cause of morbidity in patients with lipodystrophy. In nearly all cases, this results from the deposition of triglycerides within hepatic parenchyma[2] and is predominantly observed in generalised lipodystrophy due to extensive fat liberation and metabolic derangement. Such liver injury is less common in partial lipodystrophy where adipose tissue loss is limited and insulin resistance is mild.[2]

In recent years, however, reports have emerged of patients with lipodystrophy, most commonly APL, developing autoimmune hepatitis (AIH).[2–4] Unlike the liver injury caused by triglyceride deposition, the relationship between AIH and APL is poorly understood and reports describing this association are still extremely limited.[2–4] It is important that we develop a better understanding of why children with APL appear to be at risk of AIH (or vice versa) and to map their clinical characteristics. For this purpose, the authors present the following case.

CASE SUMMARY

A 17-month-old boy presented to hospital with a 3-week history of fever associated with symmetrical swelling of both legs distally. He was otherwise well with no additional infective or systemic symptoms and there was no significant family history. Examination revealed a pale, red, macular rash on his lower limbs (clinically resembling Henoch-Schönlein purpura (HSP)) which was painless and associated with non-pitting oedema. His tympanic membranes were slightly inflamed but the remainder of his examination was unremarkable. In view of his persistent fever and unusual presenting symptoms, he was admitted to hospital and underwent extensive investigations. Among these, he was noted to have a mildly raised alanine transaminase (ALT), 62 IU/L and

significantly raised C reactive protein (CRP), 129 mg/L. Although no pathogen was identified, a course of oral co-amoxiclav was initiated for acute otitis media in association with possible HSP and, following improvement in inflammatory markers, fever and rash, he was discharged home.

One month later, his limb swelling and rash had markedly improved but his fever persisted. His CRP had also risen and his ALT remained elevated (81 IU/L). An abdominal ultrasound demonstrated a smoothly enlarged liver with abnormal echotexture which raised suspicions of a liver disorder and a subsequent autoantibody screen-identified anti-LKM antibodies in his serum. A liver biopsy at this stage demonstrated mild portal fibrosis but no other histopathological abnormalities suggestive of autoimmune or any other chronic liver disease. The remainder of his work-up to exclude chronic liver diseases was unremarkable.

Within 3 months of first presentation, his fever and limb swelling had completely resolved. In fact, it was now noted that his legs were very slim and muscular and his long saphenous veins had become prominent. It quickly became apparent that this appearance had been caused by a loss of lower limb fat. While rare in this age group, the changes were characteristic of lipodystrophy and he was therefore discussed with the national severe insulin-resistance team.

During the same timeframe, a significant rise in ALT (654 IU/L), aspartate aminotransferase (AST) (386 IU/L) and gamma-glutamyl transferase (GGT) (122 IU/L) was observed but liver synthetic function remained normal. His repeat liver biopsy, now 4 months after presentation, demonstrated more convincing features of chronic active hepatitis (figure 1) and anti-LKM antibodies remained detectable in his serum. A diagnosis of AIH was confirmed and oral prednisolone was started at 2 mg/kg. This significantly reduced his transaminase levels and the addition of azathioprine (1.5 mg/kg) normalised ALT, AST and GGT within 6 months.

Throughout this time, the adipose tissue loss progressed to his upper limbs and trunk but largely spared his face and gluteal region (figure 2). He was reviewed by the insulin-resistance team and a diagnosis of APL was reached based on the extent and distribution of adipose tissue loss. In keeping with this, his triglyceride level was slightly raised (2.82 mmol/L) but fasting glucose and insulin profiles remained normal. Whole-exome sequencing did not reveal any genetic abnormality that might predispose to AIH or APL. This includes autoimmune polyglandular syndrome.[5]

Five years since his first presentation, the clinical features of lipodystrophy have persisted but have not significantly progressed. He remains on maintenance therapy of prednisolone and azathioprine and his liver bloodwork, including synthetic function, remains normal. Serial ultrasound has not demonstrated progressive splenomegaly or steatosis and repeat biopsy was undertaken at 3 years of age to decide if steroid treatment could be discontinued. This demonstrated ongoing mild-moderate portal inflammation with fibrosis but again no steatosis (figure 1). He therefore continues on dual immunosuppression.

DISCUSSION

The development of AIH in association with APL is extremely rare and this case adds to only a handful of other published reports. In this child, features of APL presented at an early age and occurred in the context of a relatively mild hepatitis making early diagnosis more challenging. Through close monitoring, regular discussion with specialist services and effective immunosuppression, we have so far been able to manage both conditions, but the question still remains: why have both conditions arisen in this child?

Multiple authors have noted that infections often precede the onset of lipodystrophy. The exact mechanism for this is unknown but it may involve the activation of autoimmunity as APL is associated with multiple other autoimmune diseases.[3] Although a pathogen was not identified in this case, it seems feasible that infection played a role in its onset given the presenting features of fever and raised CRP. Additionally, the HSP-like presentation may be further evidence for an underlying autoimmune process as HSP itself has been linked with APL previously.[4]

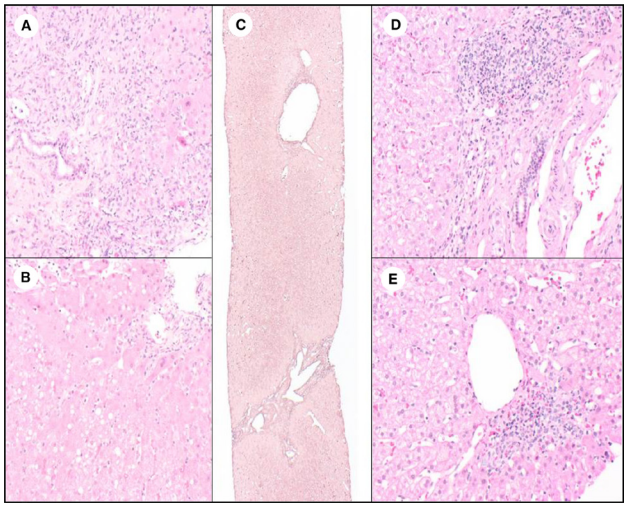

Figure 1 Liver histology. (A,B) (left) From liver biopsy in 2015 (age 20 months) showing; (A) portal inflammation with prominent interface activity as expected in autoimmune hepatitis, (B) very mild steatosis insufficient to implicate a fatty liver disease picture as might be expected in lipodystrophy. (D,E) (right) From 2018 liver biopsy (age 3 year 10 months) showing; (D) persistence of portal inflammation but near absent interface activity, (E) absence of steatosis, an aggregate of inflammatory cells is seen close to a central vein. Central panel (C) demonstrates fibrous portal tract expansion but preserved vascular relationships. Fibrotic stage, regarded as mild to moderate, did not change between the 2015 and 2018 biopsies. H&Es original magnification ×200; Orcein (central panel) original magnification ×40.

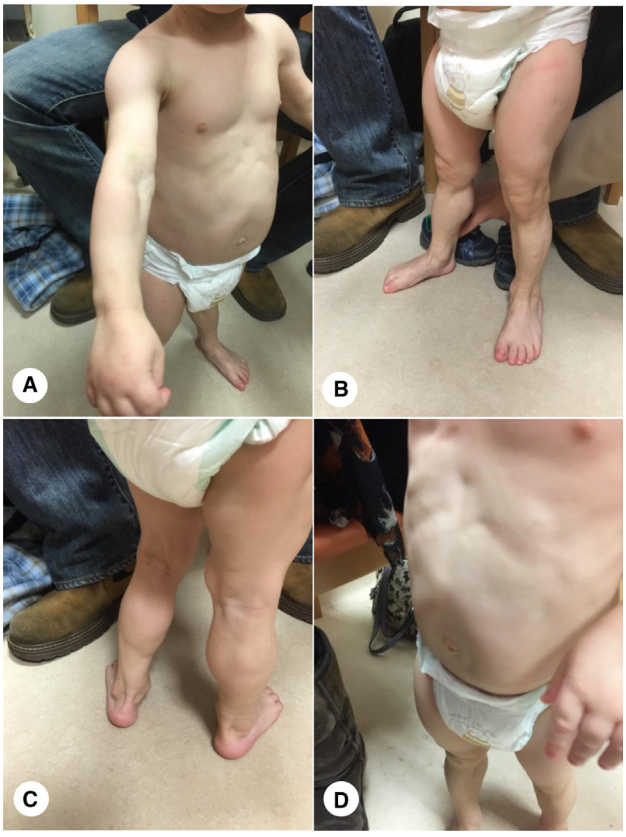

Figure 2 Photographs demonstrating the features of lipodystrophy in the case subject. (A–C) Images demonstrate the loss of adipose tissue seen in his upper and lower limbs and (D) image shows the loss of abdominal adipose tissue with visible abdominal musculature. No loss of adipose tissue was noted in the subject's face.

When considering the relationship between AIH and APL in this case, it is tempting to suggest that the signs of liver disease, namely a gradual rise in ALT, predated those of lipodystrophy. Unfortunately, the exact onset of lipodystrophy is often hard to identify as subtle features may have developed before marked changes were noted. It is therefore difficult to draw significant conclusions about disease sequence. What's more, a previous case report has observed the opposite relationship.[2] It is however interesting that the steep rise in liver transaminases coincided with the rapid emergence of lipodystrophy, adding weight to the hypothesis that the two disease processes are linked. It was reassuring that the rise in ALT/GGT was effectively reversed following immunosuppression but this was not matched by an improvement in adipose tissue distribution. Sadly, the treatment options for APL remain limited with priority focused more on disease monitoring.

In conclusion, we acknowledge that the association between AIH and APL is rare but the consequences of delaying diagnosis in either condition are significant. Until our understanding of this association strengthens, it is important for any clinician looking after children with AIH to adopt a high index of suspicion for lipodystrophy and undertake regular clinical examination, especially where there is evidence of subcutaneous fat loss.

Acknowledgements We would like to thank Darren Fowler, Elena Collantes and Eve Fryer from the Department of Cellular Pathology at Oxford University Hospital NHS Trust as well as the staff from the Department of Cellular Pathology at Birmingham Women's and Children's Hospital for their work providing histological images for this case.

Contributors This case was originally identified by GA who conceived of the idea to publish a case report. GA, AR, GG and RW have all made significant contributions to the clinical management of the case and RB provided and interpreted the liver histology. All authors contributed to the drafting and finalising of the report which was written by CB and KD and it was submitted by CB. GG and GA are the senior authors with overall responsibility for the report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Christopher Bakewell http://orcid.org/0000-0002-7402-1408

REFERENCES

1 Chiquette E, Oral EA, Garg A, *et al*. Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges. *Diabetes Metab Syndr Obes* 2017;10:375–83.
2 Ribeiro A, Brandão JR, Cleto E, *et al*. Fatty liver and autoimmune hepatitis: two forms of liver involvement in lipodystrophies. *GE Port J Gastroenterol* 2019;26:362–9.
3 Misra A, Peethambaram A, Garg A. Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. *Medicine* 2004;83:18–34.
4 Senior B, Gellis SS. The syndromes of total lipodystrophy and of partial lipodystrophy. *Pediatrics* 1964;33:593–612.
5 Sorkina E, Frolova E, Rusinova D, *et al*. Progressive generalized lipodystrophy as a manifestation of autoimmune polyglandular syndrome type 1. *J Clin Endocrinol Metab* 2016;101:1344–7.