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Proliferative diabetic retinopathy as the initial presenting feature of type 1 diabetes

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Summary

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder caused by the destruction of the pancreatic beta cells, which produce insulin. Individuals with T1DM usually require at least 3-5 years to develop microvascular complications in comparison to people with type 2 diabetes (T2DM), who may develop complications even before the diagnosis of diabetes. We discuss a patient who presented with proliferative diabetic retinopathy subsequently diagnosed with T1DM and diabetic neuropathy following investigations. Diabetic retinopathy or other microvascular complications as the presenting feature of T1DM is rarely known or reported in the literature. A 33-year-old healthcare worker had been seen by the opticians due to 1-week history of blurred vision. The ophthalmology assessment had confirmed proliferative retinopathy in the right eye and severe non-proliferative retinopathy in the left eye with bilateral clinically significant macular oedema. His BMI was 24.9 kg/m^2. The nervous system examination revealed bilateral stocking type peripheral neuropathy. The random venous glucose was 24.9 mmol/L. Plasma ketones were 0.7 mmol/L and HbA1c was 137 mmol/mol. On further evaluation, the anti-glutamic acid decarboxylase (GAD) antibody was positive, confirming the diagnosis of T1DM. He was started on aflibercept injections in both eyes, followed by panretinal photocoagulation. Subsequent nerve conduction studies confirmed the presence of symmetrical polyneuropathy. The pathogenesis of the development of microvascular complications in T1DM is multifactorial. Usually, the development of complications is seen at least a few years following the diagnosis. The occurrence of microvascular complications at presentation is rare. This makes the management challenging and extremely important in preventing the progression of the disease.

Learning points

- The pathogenesis of the development of microvascular complications in type 1 diabetes mellitus is multifactorial.
- The development of complications is seen at least a few years following the diagnosis.
- Occurrence of microvascular complications at presentation is rare.
- This makes the management challenging and extremely important to prevent the progression of the disease.

Background

Type 1 diabetes mellitus (T1DM) develops as a result of autoimmune destruction of the pancreatic beta cells. The pathogenesis is multifactorial (1). The disease develops in genetically susceptible individuals over months to years, during which the patients become positive for relevant autoantibodies but remain asymptomatic (1). The onset is possibly triggered by multiple environmental factors (1). The timing of presentation with hyperglycaemia is determined by the number of beta cells destructed by the autoimmune process and at least 60–90% loss of beta cell function is seen at the diagnosis (1).

Several mechanisms are thought to be responsible for the onset of vascular complications of the disease. Exposure to chronic hyperglycaemia is known to initiate multiple metabolic processes leading to generation

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of advanced glycation end products (AGE), reactive oxygen species (ROS) and sorbitol (2). Further, it leads to activation of diacylglycerol (DAG), beta-2 protein kinase C (PKC), the polyol pathway and renin–angiotensin system (RAS) (2).

Whilst the risk of development of vascular complications increases with the duration of the disease, optimal glycaemic control has been proven to delay the onset of microvascular complications. Presentation with microvascular complications including proliferative retinopathy or peripheral neuropathy is rare. We report a case history of a person with T1DM who has developed proliferative diabetic retinopathy and peripheral neuropathy at the presentation of the disease.

Case presentation

A 33-year-old healthcare worker presented to the opticians in April 2021 with a history of blurred vision for 1 week. He had not noticed any weight loss or osmotic symptoms. About 4 weeks prior to the presentation, he had been treated by the general practitioner for candida balanitis. He did not have a significant past medical history and had not been on long-term medications. Our patient did not have a family history of diabetes. He had received the first dose of the coronavirus disease 2019 (COVID-19) mRNA vaccine (Pfizer-BioNTech) in January 2021 and the second dose in March 2021.

On examination, he was averagely built with a BMI of 24.9 kg/m^2. His blood pressure was normal at 130/92 mmHg. Ophthalmological examination was consistent with proliferative retinopathy of the right eye and severe non proliferative retinopathy of the left eye with bilateral macular oedema. There were bilateral posterior pole dot and blot haemorrhages and central macular exudates. Vessel calibre appeared normal and no signs of ischaemia/cotton wool spots were noted to suggest retinal hypertension. The optic disc also appeared distinct (Fig. 1).

The nervous system examination revealed bilateral stocking type of peripheral neuropathy up to mid-thigh. Upper limb examination was clinically nonsignificant. His cardiovascular, respiratory and abdomen examinations were normal.

Investigations

He was admitted to the hospital with a random blood glucose of 24.9 mmol/L and serum ketone level of 0.7 mmol/L. The HbA1c was 137 mmol/mol and the

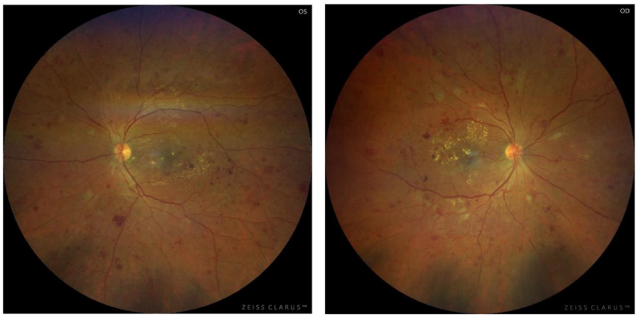

Figure 1
Fundoscopy demonstrating bilateral proliferative retinopathy. There were bilateral posterior pole dot and blot haemorrhages and central macular exudates. Vessel calibre appeared normal and no signs of ischaemia/cotton wool spots were noted to suggest retinal hypertension. The optic disc also appeared distinct.

anti-glutamic acid decarboxylase (GAD) antibody was positive, confirming the diagnosis of T1DM. His initial laboratory tests showed normal renal, liver and thyroid profiles and the results are summarised below (Table 1). He did not have any routine investigations prior to the presentation.

Nerve conduction studies confirmed the presence of a large-fibre, sensory more than motor, axonal, length-dependent peripheral neuropathy compatible with symmetrical diabetic polyneuropathy (Fig. 2).

Treatment

The patient was started on a variable rate intravenous insulin regimen, which was later converted to a subcutaneous basal bolus regimen. He was discharged home four days after the admission with Lantus 12 units once daily and NovoRapid 4–6 units with meals. With the insulin, he maintained the capillary glucose between 7 and 15 mmol/L. He was provided with education and training for self-management of diabetes prior to the discharge. Following an urgent ophthalmology referral, he was started on anti-VEGF (Aflibercept) injection to both eyes followed by panretinal photocoagulation of the right eye and prophylactic retinal photocoagulation of the left eye.

After 3 months of initiating insulin and optimising the glycaemic control, he developed a large vitreous haemorrhage in the right eye, which needed urgent assessment and intervention by the Ophthalmologist.

Outcome and follow-up

His HbA1c was 52 mmol/mol after 6 months of initiation of insulin. Ophthalmology assessment following 9 months

Table 1 Investigation summary.

Investigation	Result	Reference range
Random blood glucose, mmol/L	24.9	4–11
Serum ketones, mmol/L	0.7	0–0.6
HbA1c, mmol/mol	137	20–41
Anti-GAD antibody, IU/mL	97	0–10
IA2 antibody, IU/mL	<10	0–10
White cell count, 10^9/L	4.9	3–11
Haemoglobin, g/L	139	130–180
Platelets, 10^9/L	222	150–400
UACR, mg/mmol	<2	<2.9
Serum sodium, mmol/L	137	133–146
Serum potassium, mmol/L	4.5	3.5–5.3
Serum creatinine, µmol/L	62	64–104
eGFR, mL/min/1.73 m^2	>90	90–120
Blood urea, mmol/L	5.5	2.5–7.8
Bicarbonate, mmol/L	24	22–29
Serum adjusted calcium, mmol/L	2.31	2.1–2.6
Alanine transaminase, U/L	34 U/L	<41
TC, mmol/L	5.4 mmol/L	2.5–6.0
HDL-C, mmol/L	1.0	1.1–2.4
Triglycerides, mmol/L	1.3	0.5–4.5
LDL-C, mmol/L	3.8	1.0–4.0
TC/HDL-C ratio	5.4	<5.0
TSH, mU/L	1.77	0.3–4.5
Serum total testosterone, nmol/L	15.2	9.0–29.0

GAD, glutamic acid decarboxylase; IA2, islet antigen 2; UACR, urine albumin creatinine ratio; eGFR, estimated GFR; TC, total cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol.

of diagnosis showed improved macular oedema and no further progression of retinopathy.

Discussion

T1DM is a chronic disease comprised of genetic, autoimmune and environmental aetiology (1). Usually, the development of the disease occurs in a genetically predisposed individual with autoimmunity triggered by multiple environmental factors (1). When compared to the people with type 2 diabetes, who have a significant family history in the first degree relatives (87.8–94.5%), only 10–15% of people with T1DM have a first or a second-degree relative affected by the disease (1, 3). Genome wide association studies have detected more than fifty genetic loci predisposing to the development of T1DM (4). Out of those, the majority of genes called 'Human Leucocyte Antigen' (HLA) are detected in the major histocompatibility complex (MHC) region on chromosome 6 (1). Furthermore, environmental and genetic factors such as mutation in the AIRE gene (AutoImmune REgulator) can set off the autoimmune process in the body (1). Our patient did not have a family history of T1DM.

Sensory Nerve Conduction:

Nerve and Site	Onset Latency	Peak Latency	Amplitude	Segment	Latency Difference	Distance	Conduction Velocity
Superficial peroneal.R							
Ankle	NR ms	NR ms	NR µV	Dorsum of foot-Ankle	ms	mm	m/s
Sural.R							
Lower leg	2.5 ms	ms	3 µV	Ankle-Lower leg	2.5 ms	100 mm	40 m/s
Median.R							
Digit III (long fing	2.7 ms	3.2 ms	10 µV	Wrist-Digit III (long finger)	2.7 ms	138 mm	51 m/s
Digit II (index fing	2.7 ms	3.1 ms	7 µV	Wrist-Digit II (index finger)	2.7 ms	142 mm	53 m/s
Ulnar.R							
Digit V (little fing	2.4 ms	ms	2 µV	Wrist-Digit V (little finger)	2.4 ms	107 mm	45 m/s

Motor Nerve Conduction:

Nerve and Site	Latency	Amplitude	Area	Segment	Latency Difference	Distance	Conduction Velocity
Peroneal.R							
Ankle	4.2 ms	3.0 mV			ms	mm	m/s
Fibula (head)	13.9 ms	1.4 mV	58.2	Ankle-Fibula (head)	9.7 ms	355 mm	37 m/s
Tibial.R							
Ankle	5.6 ms	10.2 mV			ms	mm	m/s
Median.R							
Wrist	4.0 ms	15.2 mV			ms	mm	m/s
Elbow	9.2 ms	14.9 mV	105.9	Wrist-Elbow	5.2 ms	280 mm	54 m/s

F-Wave Studies

Nerve	M-Latency	F-Latency	F-M Latency
Tibial.R	3.8	55.0	51.2

Figure 2
No sensory response was obtainable from the right superficial peroneal nerve. A sensory study of the right sural nerve shows a normal conduction velocity but with reduced amplitude. Sensory studies of the right median nerve show reduced amplitude for age but normal conduction velocity. A sensory study of the right ulnar nerve stimulating digit 5 shows a reduced amplitude and slight reduced conduction velocity. A motor study of the right median nerve is normal. A motor study of the right common peroneal nerve shows a normal conduction velocity but with reduced amplitude for age. The compound muscle action potential (CMAP) from the right posterior tibial nerve is reduced in amplitude. F wave responses are normal. In conclusion, these results are consistent with a large-fibre, sensory more than motor, axonal, length-dependent peripheral neuropathy.

Defects in immune responses which are naturally designed to eliminate auto reactive lymphocytes can result in multiple autoimmune diseases including T1DM (1). Though the trigger of the autoimmune

response is still unclear, viruses, nutrients and toxins are thought to play a role (1). Viral infections activating innate immune responses and molecular mimicry, as well as certain vaccinations are thought to initiate the development of autoimmune diseases including T1DM (1). Despite not having clear evidence of the pathophysiology of the development of T1DM following the COVID-19 vaccination, several case series and case reports published in the literature have demonstrated a possible association (5, 6). Therefore, it is important to highlight that our patient had his first COVID-19 vaccination about 3 months and the second vaccination about 2 weeks prior to the presentation.

It is understood that the interplay between cellular and humoral immunity results in an exaggerated immune response of the body, which leads to the development of the T1DM. Destruction of the β-cells of the endocrine pancreas by apoptosis is mediated by caspase (cysteine asparaginase activations) cascade which is activated by inflammatory cytokines such as Interleukin 1 (IL-1), tumor necrosis factor-α and interferon-γ released by T lymphocytes forming the cellular immune response (1). Furthermore, another theory suggests that β-cell destruction occurs directly by the autoimmune action of the T lymphocytes. Humoral immunity is mediated by the autoantibodies implicated in the development of T1DM. They include anti-glutamic acid decarboxylase (GAD) antibodies, tyrosine phosphatase related islet antigen 2 (IA-2) antibodies, insulin autoantibodies (IAA) and zinc transporter (ZnT8) antibodies. The anti-GAD can be seen in about 70% of patients at the presentation whilst IA-2 antibodies are found in 60% of patients at diagnosis. IAA and ZnT8 antibodies can be detected even many years before the diagnosis (7). Our patient was positive for anti-GAD antibodies at the presentation.

It is uncommon for a person with T1DM to present with microvascular complications at the diagnosis. Nevertheless, the presence of anti-GAD antibodies confirmed the diagnosis of T1DM in our patient. When the initial clinical presentation is not typical of T1DM, other causes for retinopathy should be considered. The possible causes are hypertensive retinopathy, radiation retinopathy and vascular occlusive disease such as branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and ocular ischemic syndromes. Rarely, infections, paraneoplastic retinopathies, muscular dystrophies, craniofacial disorders, inflammatory diseases and autoimmune diseases could present as ophthalmological manifestations (8).

Macrovascular and microvascular complications associated with diabetes mellitus contributes to the disease morbidity and mortality. The intensive glycaemic control from the onset of the disease can prevent and delay macrovascular and microvascular complications, demonstrated by the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study in patients with T1DM (9, 10). Our patient had advanced microvascular disease including proliferative retinopathy and symmetrical peripheral neuropathy depriving him of the advantages of early intensive glycaemic control (10).

Combination of chronic hyperglycaemia, organ-specific and genetic factors contribute to the development of vascular disease in diabetes. Exposure to chronic hyperglycaemia is known to initiate multiple metabolic processes leading to generation of AGE, ROS and sorbitol (2). Furthermore, it leads to activation of DAG, PKC, the polyol pathway and RAS (2). In the kidneys, above mentioned aberrant metabolic products and pathways leads to activation of pro-inflammatory and pro-fibrotic gene expression contributing to diabetic nephropathy combined with altered glomerular haemodynamics (11). Structural and functional alterations in the kidneys include glomerular hyperfiltration, glomerular and tubular epithelial cell structural changes and dysfunction leading to development of microalbuminuria. Subsequently, the thickening of the glomerular basement membrane, accumulation of extracellular matrix and hypertrophy of mesangial cells lead to overt proteinuria and glomerulosclerosis finally leading to end stage renal disease (12). It is unknown whether the onset and the progression of diabetic nephropathy is related to the type of diabetes. Nevertheless, thickening of the glomerular basement membrane is seen as early as within the first year of T1DM diagnosis (13). Our patient had a normal urinary albumin excretion and a normal eGFR at presentation. However, it is necessary to monitor him closely for the development of diabetic nephropathy due to the presence of other microvascular complications at the presentation.

Diabetic retinopathy is the main cause of visual loss in adults (14). Retinal microvascular changes, inflammation and neuro-degeneration is involved in the pathogenesis of the disease (15). The earliest vascular changes are vascular dilatation and changes to the blood flow (15). Pericyte loss and microaneurysm formation is seen early in the disease (16). Impairment

of the blood retinal barrier is further contributed by the endothelial cells apoptosis and basement membrane thickening (16). All of these changes contribute to occlusion of retinal capillaries, ischemia and subsequent neovascularisation is the hallmark of proliferative diabetic retinopathy (15). In addition to the above mentioned pathophysiological mechanisms, genetic factors are known to contribute to the severity of diabetic retinopathy (10). Our patient did not have a family history of diabetic retinopathy in the first degree relatives. It is also known that the risk of retinopathy increases with the duration of diabetes (17). Vision threatening diabetic retinopathy is found to be rare in patients with T1DM within the first 3–5 years of the disease and almost all the patients tend to develop eye disease during the next twenty years (18). Our patient had evidence of proliferative retinopathy and clinically significant macula oedema at the diagnosis. A presentation of T1DM with such advanced diabetic retinopathy is not documented in the literature. Furthermore, the absence of typical osmotic symptoms at presentation may suggest the possibility of slow onset disease with a prolonged asymptomatic phase as seen in people with latent autoimmune diabetes (aka LADA). Insulin resistance or mixed type 2 diabetes mellitus would need to be considered in such presentations. However, as our patient achieved a good glycaemic control with a relatively a low dose of insulin, insulin resistance is unlikely. Furthermore, though there is a significant association between diabetic retinopathy and nephropathy described in the literature, our patient had bilateral proliferative diabetic retinopathy without evidence of diabetic nephropathy (19).

The commonest presentation of diabetic neuropathy is distal symmetric polyneuropathy as in our patient (20). Multiple pathways are involved in the pathogenesis of diabetic neuropathy. They contribute to mitochondrial dysfunction, oxidative and ischemic damage. In addition, there is a failure of nerve fibre repair in a fibre selective manner that favourably affects the distal sensory and autonomic fibres (21, 22). Major risk factors for neuropathy are older age and the duration of diabetes (23). Neither the age nor the duration of diabetes in our patient match the risk factors for neuropathy.

The worsening of diabetic retinopathy following the rapid improvement of glycaemic control is well known. The DCCT trial observed initial worsening of retinopathy in significantly more patients assigned to receive intensive (13.1%) vs conventional (7.6%) treatment ($P < 0.001$) (9). Following 3 months of initiation of treatment and achieving a good glycaemic control, our patient developed a large vitreous haemorrhage in the right eye, which needed urgent intervention by the ophthalmologist. After 6 months of the diagnosis, his HbA1c was 52 mmol/mol and ophthalmology assessment after 9 months showed improvement of macular oedema and no further progression of neovascularisation hence demonstrating the beneficial effects of optimisation of glycaemic control.

This case highlights an uncommon presentation of a patient with T1DM complicated by proliferative retinopathy and distal symmetrical polyneuropathy at the time of diagnosis. Although rare, it is important to be aware of such presentations, as early detection of complications and appropriate treatment may delay the progression of the disease. Furthermore, appropriate patient education and optimising the glycaemic control from the outset can lead to prevention and halt the progression of complications associated with diabetes. Further study of similar case reports and detailed research will be useful in the future to determine the pathogenesis of such rare occurrences.

Conclusions

In conclusion, we have described a patient presenting with proliferative retinopathy and distal symmetrical neuropathy at the diagnosis of T1DM. The awareness of such presentations are important for the early detection of complications of T1DM and to optimise the management.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case study reported.

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Availability of data and material
Clinical details and results of investigations are documented in bed head tickets. Bed head tickets are available in the record room of the West Cumberland Hospital, Whitehaven, North Cumbria Integrated Care, NHS Foundation Trust of United kingdom.

Patient consent
Patient's consent was taken to report his clinical details anonymously. We have taken the informed written consent from the patient to report and publish about his illness anonymously.

Author contribution statement

IR and CI were involved in the history taking, examination, diagnosing and management of patient's condition and prepared the manuscript for publication. Both authors read and approved the final version of the manuscript.

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