

## Case Report

## Heterozygote Patient with Tangier Syndrome and Coronary Artery Disease

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Disturbances of lipid metabolism form a group of diseases that cause a change in the quantity of lipids in the blood or an alteration in their composition. Tangier syndrome belongs to this category and is a rare disease of genetic origin that alters the composition of high density lipoproteins (HDL) in the plasma. The syndrome manifests itself through low levels of HDL, low density lipoprotein (LDL) and total cholesterol and elevated levels of triglycerides. Because of the increased deposition of cholesterol esters in the cells, there is swelling of the tonsils with the appearance of characteristic orange-coloured maculae, swelling of the spleen and in some cases also of the liver.

We present the case of man of Greek origin, 67 years old, who came to our hospital because of episodes of paroxysmal atrial fibrillation and concomitant chest pain. The general laboratory tests showed low levels of HDL, LDL and total cholesterol. A more careful examination of the mouth and fauces revealed the orange maculae characteristic of the syndrome. The diagnosis was confirmed by measuring the patient's A1 serum apolipoprotein concentration, which was significantly below the normal limits and at levels corresponding to the heterozygotes of Tangier syndrome. We also take the opportunity to present a short review of the relevant literature.

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**T**angier syndrome is a rare syndrome of genetic origin that causes disturbances of lipid metabolism. Around 70 cases have been described in the literature.<sup>1</sup> The genetic damage results in a reduction of cholesterol excretion by the peripheral cells. The syndrome is manifested through low levels of high density lipoprotein (HDL) and total cholesterol and elevated triglyceride levels.<sup>2,3</sup> The increased deposition of cholesterol esters it causes in the cells of the reticuloendothelial system leads to swelling of the tonsils, the spleen and in some cases the liver.<sup>4,5</sup> In heterozygotes of the syndrome the clinical manifestations are milder and the lipidaemic profile is less affected.<sup>2</sup> Homozygotes and heterozygotes have a greater risk of coronary artery disease.<sup>6</sup>

### Case description

A 67-year-old man came to our hospital because of episodes of paroxysmal atrial fibrillation and concomitant chest pain. The clinical examination showed no pathological findings. Heart sounds were normal, without extra sounds or murmurs, and the respiratory sounds were also physiological. Chest X-ray showed normal lung fields and cardiothoracic index 50%. The patient's history contained similar anginal episodes that had been diagnosed as due to coronary artery disease after cardiac catheterisation carried out 2 months previously. The catheterisation found that the main branch of the left coronary artery was free of stenoses, the anterior descending branch was an

atheromatous vessel without stenoses, whereas the circumflex artery was obstructed after the origin of the great marginal artery. The right coronary artery was an atheromatous vessel with 85% stenosis in the first third. Left ventriculography showed a ventricle with normal size and contractility and an ejection fraction of 50%. The diagnosis was thus 2-vessel coronary artery disease with good left ventricular function. The patient had also undergone a cataract repair procedure in both eyes. His family history was uneventful, while the patient himself was the father of 2 children, aged 25 and 27 years, who had no particular health problems.

Laboratory exams gave the following: WBC 6200/uL, RBC  $5.05 \times 10^6$ /uL, Hb 15.2 mg/dl, Ht 45.5%, platelets 219000/uL, 1 hour ESR 40 mm, glucose 147 mg/dl, urea 57 mg/dl, uric acid 6.7 mg/dl, creatinine 1.2 mg/dl, cholesterol 120 mg/dl, triglycerides 182 mg/dl, HDL 28 mg/dl, LDL 55 mg/dl, CPK 65 U/l, LDH 316 U/l, SGOT 18 U/l, SGPT 18 U/l, K 4.6 mmol/l, Na 143 mmol/l and Ca 9.6 mg/dl.

As the laboratory exams show, the patient had markedly low levels of both HDL (28 mg/dl or 0.725 mmol/l, versus normal levels  $>45$  mg/dl or 1.166 mmol/l) and LDL (55 mg/dl or 1.425 mmol/l, versus normal levels  $110 \pm 33.5$  mg/dl or  $2.84 \pm 0.87$  mmol/l), with levels of total cholesterol 120 mg/dl or 3.103 mmol/l (normal levels  $<200$  mg/dl or  $<5.172$  mmol/l) and triglycerides 182 mg/dl or 2.054 mmol/l (normal levels  $<200$  mg/dl or  $<2.258$  mmol/l). These results raised the question of whether the patient might have Tangier syndrome and sparked further examinations in order to validate the diagnosis.

Examination of the mouth and fauces revealed a series of orange-coloured maculae up to 0.5 cm in diameter, without swelling of the tonsils (Figure 1).

An ultrasound examination of the upper abdomen showed liver dimensions within normal limits with fatty infiltration, without pathological findings from the biliaries, while the spleen also had normal dimensions, as did the remaining organs, pancreas and kidneys. Cardiac ultrasound showed a normal-sized left ventricle with physiological wall thickness and good contractility with an ejection fraction around 60%. The left atrium was within normal limits. The cardiac valves showed no organic lesions and the Doppler study found no indications of pathological flow.

In addition, an ophthalmological evaluation was sought in order to determine any ophthalmic damage. The visual acuity test was physiological, while



**Figure 1.** Photograph of the patient's mouth. The arrow indicates three orange maculae on the left tonsil, about 5 mm in diameter. These maculae have been described as a manifestation of Tangier syndrome in the international literature and are caused by the deposition of cholesterol esters in the cells of the reticuloendothelial system.

there was bilateral aphakia with an intraocular lens in the posterior chamber as a result of the cataract correction procedure. Examination of the fundus showed bilateral peripheral detachment of the vitreous, without damage to the optic nerve or blind spot. However, on the periphery of the fundus of the left eye at around 9 o'clock there was a pigmentation deposit about  $1\frac{1}{2}$  papilla in diameter which was evaluated as a nevus.

A test of thyroid function was then carried out to rule out hyperthyroidism, and physiological values of TSH and thyroid hormone were found: TSH: 0.465  $\mu$ IU/ml (normal values: 0.4  $\mu$ IU/ml-4  $\mu$ IU/ml), T3 92.7 ng/dl (normal values: 65 ng/dl-170 ng/dl), TT4 10.3  $\mu$ g/dl (normal values: 5.2  $\mu$ g/dl-12.5  $\mu$ g/dl). The patient was not taking any medication that could cause a drop in HDL (cortisone, non-selective  $\beta$ -blockers) and his renal function was physiological. Secondary hyperlipidaemias which involve low HDL levels were therefore also ruled out from the diagnosis.

The diagnosis was validated by measurements of apolipoprotein A1 (apo-A1) levels in the serum, which are reduced in individuals with Tangier syn-

drome. Our patient had an apo-A1 concentration of 0.79 g/dl (normal values 1.17 g/dl-1.69 g/dl). Taking into account the clinical and laboratory findings and comparing them with the international literature led to a diagnosis of Tangier syndrome of heterozygotic type with coronary artery disease.

Since the syndrome is due to a recessive autosomal gene, both the patient's children were examined for any indications of the syndrome, so that appropriate genetic counselling could be provided. The general examination was negative (HDL 78 mg/dl or 2.02 mmol/l, and 69 mg/dl or 1.787 mmol/l for the two children) so no more specific examinations were performed.

The patient's syndrome was explained to him, the treatment he was receiving for coronary artery disease was adjusted and he was given instructions about physical exercise and a low-fat diet.

## Discussion

Tangier syndrome is a member of a group of disorders affecting HDL lipoprotein metabolism. It is a rare syndrome of genetic origin. It was seen for the first time in residents of Tangier island, off the coast of Virginia, and around 70 cases have been described in the literature.<sup>1</sup> It is transmitted through the recessive autosomal type and is characterised by low levels of Apo-A1, HDL, LDL and total cholesterol.<sup>2,3</sup> The increased deposition of cholesterol in the tissues of the reticuloendothelial system causes swelling of the liver and spleen and hypertrophic orange-yellow tonsils. Cases of Tangier syndrome have also been described that affected the eyes (ectropion, corneal infiltration, loss of vision) and the peripheral nervous system (limb weakness and facial diplegia). However, there have been cases of homozygotic Tangier syndrome described in the literature with few of the above clinical signs.<sup>4,5</sup> The syndrome is a predisposing factor for the early development of coronary artery disease.<sup>6</sup>

In the case of heterozygotes there are few studies available, but from these it appears that the clinical picture in heterozygotes differs from individual to individual, while their lipidaemic profile is clearly less affected compared with homozygotes of the syndrome.<sup>2</sup> As regards the risk of coronary artery disease,

it appears that this is three times as likely as in a healthy population.

Tangier syndrome is due to a mutation in the ABC1 gene (ATP-binding cassette – 1), which is located on chromosome 9q31.<sup>1</sup> Normally, this gene is responsible for the synthesis of a protein on the surface of the cells, through which cholesterol is eliminated from the peripheral cells and taken up by Apo-A1.<sup>1</sup> In this way the disc-shaped HDL<sub>3</sub> lipoprotein molecule is formed. In lipoprotein HDL<sub>3</sub> the LCAT enzyme acts, esterizing the absorbed cholesterol and leading to the formation of the spherical HDL<sub>2</sub> lipoprotein molecule, which transports the cholesterol to the liver cell so that it may be eliminated with the bile. In the case of Tangier syndrome, however, because of the mutation of the gene, the cholesterol is not eliminated by the cells. This leads to the formation of HDL lipoprotein that has a low cholesterol ester content. It has been observed that when HDL lipoprotein is low in cholesterol esters it is unstable and quickly breaks down together with Apo-A1 in the peripheral blood.<sup>6</sup> The breakdown products are eliminated by the kidneys. In this way we can interpret the accumulation of cholesterol esters in the cells of the reticuloendothelial system, the biochemical profile and the increased risk of coronary artery disease in those suffering from Tangier syndrome.

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