# Tangier disease: a case report

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**Abstract**

Tangier disease is an extremely rare genetic disease (incidence estimated of 1/120.000.000 individuals, with less than 100 cases reported worldwide), characterized by severe deficiency of high-density lipoproteins (HDL). The clinical features of this disease are due to an increase on cholesterol esters accumulation in the affected tissues and no known therapy alters the course of Tangier Disease.

We describe a clinical case of a 58 year old man, referred to Internal Medicine for the evaluation of very low total cholesterol, which study led to the diagnosis of Tangier Disease, with clinical findings of splenomegaly and hypersplenism.

The authors present a brief review of this disease.

Key words: Tangier, hypoalphalipoproteinaemia.

## INTRODUCTION

Tangier Disease, described in 1961 by Fredrickson, is a genetic recessive autosomal disease, secondary to a deletion of a gene basis ABCA1 in the chromosome 9 (9q31), resulting in an inadequate synthesis of a regulating protein of cholesterol efflux. In the complex lipidic metabolism, such protein has the role of carrying the intracellular transmembrane cholesterol, accumulated in the cells of the reticuloendothelial system (monocytes and macrophages), to high density lipoproteins (apolipoprotein A1 and HDL), carrying it subsequently to the liver.[1-6]

The heterozygotes for this mutation show in general just asymptomatic analytical changes (HDL cholesterol below the 25 percentile), while the homozygotic usually show a clinical setting of systemic attainment, very low HDL cholesterol (usually below 10 mg/dL) and a much reduced apoliprotein A1 (usually below 5 mg/dL). There is a wide clinical and laboratorial heterogeneity *(Tables I and II)*, being most patients in general asymptomatic until approaching the age of 50 years old, time in which the growth of the affected organs and/or early cardiovascular disease can show symptoms.[7-9]

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## CLINICAL CASE

The authors present the case of a White man, 58 years of age, born and residing in Castelo de Paiva, referred to an Internal Medicine appointment due to asymptomatic hypocholesterolaemia (total cholesterol of 42 mg/dL and HDL cholesterol < 5 mg/dL).

He is a public service retired worker (cleaner), keeping smoking habits (15 packs year) and a history of excessive alcohol consumption in the past (150 g of alcohol/day), being milder at present. He has a history of anemia of a non clear cause at 4 years of age and paludism at 22, during his military service in Africa, without any other family background and without a regular physician follow-up.

From the family history it is mentioned the father died suddenly at 83 years of age, and the mother at 78 due to an unknown reason (suffering of diabetes mellitus and non characterized dislipidemia). He has four brothers with ages ranging from 60 to 65 years of age, whose history is unknown and could not be evaluated. He has 5 children with ages ranging from 18 to 27 years of age, and it was only possible to evaluate two daughters, one of 30 years of age with a normal lipidic profile and without evidence of a clinical disease and another daughter, 23 years of age, assessed in the Internal Medicine consultation by idiopathic thrombocytopenia, with a lipidic profile with a slight decrease on high density cholesterol (HDL 24mg/dL) and apolipoprotein A1 (99mg/dL), the rectum mucosa biopsy has revealed "foamy" cytoplasm macrophages, without any other manifestation of the disease so far, being probably a heterozygotia for Tangier Disease. The other children did not want to undergo any clinical or laboratorial evaluation.

**Table I**

**Analytical changes found in Tangier Disease**

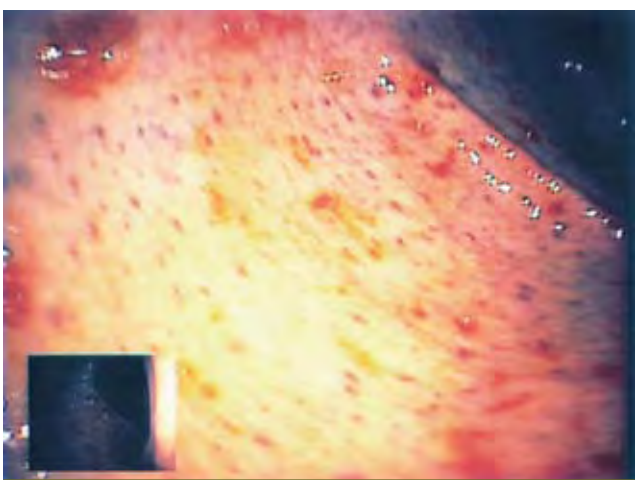
| | |
|---|---|
| Analytical changes | Low cholesterol level (total, HDL and LDL)<br>Low level of A1 and A2 apoliproteins<br>High level of chylomicrons<br>Infiltration of foamy cells in the affected tissues cells<br>Pancytopenia |

**Table II**

**Tangier Disease Clinical Manifestations**

| | |
|---|---|
| Clinical Manifestations | Tonsil hypertrophy, orangy color<br>Reduced visual acuity<br>Hepatomegaly<br>Splenomegaly<br>Lymphadenopathy<br>Neuropathy<br>Early vascular disease (cardiac and cerebral) |

At the initial assessment, the patient was asymptomatic without any ophthalmologic, ENT, neurologic or haematologic complaint, without paresthesia, or feeling of fullness, without blood losses or mucocutaneous hemorrhagic manifestations. The objective exam was to note obesity (BMI of 31.2 kg/m$^2$), oropharynx without changes, splenomegaly with palpable spleen around 8 cm below the costal edge and a normal neurological exam.



Colon aspect in the endoscopy.

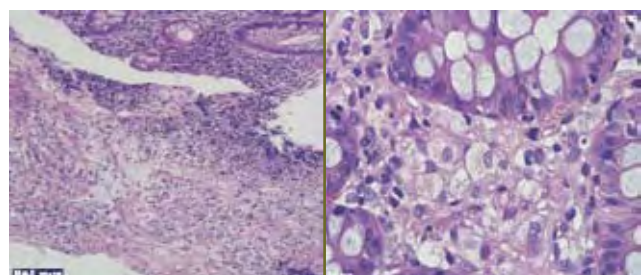
**FIG. 1**

**Table III**

**The patient analytical values, on the Internal Medicine appointment**

| | |
|---|---|
| Hb (13-17 g/dL) | 14,8 |
| MCV (80-100 fL) | 103 |
| Leukocytes (4-10 x $10^9$/L) | 4,9 |
| Platelets (150-400 X $10^9$ /L) | 45 |
| Bilirubin (0,2- 1,2 mg/dl) | 1,4 |
| Total Cholesterol (≤ 170mg/dL) | 42 |
| HDL Cholesterol (≥55mg/dL) | 3 |
| Triglycerides (≤ 150 mg/dl) | 224 |
| A1 Apolipoprotein A1 (110-205 mg/dl ) | < 4,97 |
| Vitamin B12 (189-883 pg/ml) | 325 |
| Folic Acid (3-20 ng/ml) | 4,2 |

The analytical study *(Table III)* has shown a very low total cholesterol, undetectable HDL cholesterol and apolipoprotein A1, thrombocytopenia (45 X $10^9$ /L platelets, without aggregation), mild hyperbilirubinemia (indirect) and undetectable haptoglobin. He showed no relevant laboratorial changes, without having namely a vitamin B12 deficit or folic acid, attaining other haematologic cell lines (besides platelets), with negative Coombs test both direct and indirect, and peripheral blood swabs without changes, and also no changes on the liver biochemistry or evidence of liver disease. He underwent abdominal ultrasound (massive homogeneous splenomegaly with a 20cm



Microscopic images of the colon biopsy. On the left, image of the colon mucosa infiltration by foamy cells, visible in a wider magnification of the right side image.

**FIG. 2**

**Table IV**

**Main differential diagnosis of primary hypoalphalipoproteinaemia**

| Disease | Route of transmission | Lipidic profile | Clinical manifestations |
|---|---|---|---|
| Family Hypoalphalipoproteinaemia | AD<br>Gene apo A-I mutation | HDL ↓↓↓<br>CT and LDL N ou ↑ | Early cardiovascular disease |
| HDL family deficiency | AD<br>Gene ABCA 1 mutation | HDL ↓↓↓<br>CT and LDL ↓ | Biochemical profile resembling Tangier, without any other systemic alterations |
| Tangier Disease | AR<br>Gene ABCA 1 mutation | HDL ↓↓↓<br>CT and LDL ↓ | Tonsil hypertrophy, orangy color<br>Reduced visual acuity<br>Hepatomegaly<br>Splenomegaly<br>Lymphadenopathy<br>Neuropathy<br>Early vascular disease |
| Lipoprotein deficiency Lipase | AR | CT N ↑<br>HDL↓<br>TG ↑↑↑ | Hyperlipidaemia dependent |
| Total LCAT deficiency Lecithin Cholesterol Acyl Transferase | AR<br>Gene LCAT Mutation | CT N ↑↑<br>HDL ↓↓<br>TG ↑↑ | Premature cardiovascular disease<br>Severe nephropathy<br>Anemia<br>Cornea opacity |
| Fish eye disease | AR<br>Gene LCAT Mutation | CT N ↑↑<br>HDL ↓↓<br>TG ↑↑ | Cornea opacities |

AD- dominant autosomal; AR- recessive autosomal; CT- total cholesterol; HDL- high density lipoproteins; LCAT- lecithin-cholesterol acyltransferase; LDL- low density lipoproteins, N- normal; TG- triglycerides; ↑ - increased, ↓ - reduced

spleen on a longitudinal axis), upper gastrointestinal endoscopy (gastric body xanthoma, without a biopsy) and colonoscopy (intestinal mucosa with a diffuse spider aspect, *Fig. 1*, with a biopsy revealing histiocytes of foamy cytoplasm in the mucosa and mucosa muscularis, *Fig. 2*). The ophthalmologic evaluation has shown a diffuse opacity of the cornea stroma. To achieve a screening of early cardiovascular disease were carried out an electrocardiogram, stress test and neck vessels echo-Doppler showing no changes.

The lipidic profile associated to the reminder of the condition described enabled to reach a Tangier Disease diagnosis.

The patient is still being followed up in the Internal Medicine appointment, having had as intercurrence (at 56 years old) a right lacunar vascular cerebral accident, with a deficit total recovery (sensorial). Although with some hesitation, due to the mentioned haematologic changes, there was anti-aggregation with acetyl salicylic acid for a few months.

At present, asymptomatic hypersplenism remains (with platelets values around 40 X $10^9$ /L and leukocytes around 3.5 x $10^{12}$ /L), with just an indication to comply with hygiene and diet measures (alcoholic and smoking abstinence, regular physical exercise and a diet poor in fat).

## DISCUSSION

Tangier Disease is an extremely rare entity, with very few cases described in the world and we think it is not yet described in Portugal. It has wide clinic heterogeneity, reason why some authors refer that each new case of this disease can supply vital information for its deeper knowledge and the understanding of the cholesterol efflux mechanisms.[8-9]

Other genetic diseases should be considered in the differential diagnosis of hypoalphalipoproteinaemia *(Table IV)*, situations of insulin resistance (obesity, diabetes mellitus), drugs (beta blockers, benzodiazepines, anabolizing steroids, etc.) vegetarianism, neoplasms, hepatopathies, infections and kidney failure.

In the clinical case presented, in spite of considering that the genetic study would be important (for the patient and the family) this is not performed in any Portuguese laboratory, as far as we are aware of, being only made at international level, in the context of clinical investigation. Normal neurologic and ENT tests do not exclude the diagnosis, as such changes are present in less than 50 and 20% of patients, respectively. Before so expressive laboratorial values (very low total cholesterol, HDL and apolipoprotein A1 and normal triglycerides), in the presence of splenomegaly without portal hypertension, of suggestive ophthalmologic changes and anatomopathological findings of foamy cells infiltrates in the biopsied intestine, we can state a Tangier Disease diagnosis, as none of the causing diseases of hypoalphaliproteinemia shows itself this way.

The association of this entity with early cardiovascular disease is not clear, as in spite of the high density cholesterol deficit being establish as a vascular risk factor, these patients have also very low values of low density cholesterol lipoproteins. Obviously, classic risk factors (age, gender, smoking, diet, lack of physical exercise), can also contribute to a cardiovascular disease, being its control the only therapeutic attitude recognized so far for all these patients.

There are some isolated descriptions of starting hypolipemiant therapy in such patients, with improvement of the endothelial function, increasing high density cholesterol or apolipoprotein A1.[10] Regarding hypersplenism, there are two described cases of splenectomy, with clinical worsening after surgery, with abdominal deposits of foamy cells with a high content of lipids (sometimes mimicking abdominal tumors), reason why (according to these authors) splenectomy is counter-indicated in such patients.[11-12]

From what is known of this disease, it is recommended in its management to start hygiene-dietetic measures and control of risk factors of classic vascular risks.[11-12]

These patients prognosis seems to depend on the presence of early cardiovascular disease. ■

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