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Case Report

Unusual Mild Phenotype Presentation in an Elderly Patient with Homozygous Tangier Disease

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Abstract: Tangier disease (TD) is an extremely rare inherited disorder involving lipoprotein metabolism and high-density lipoprotein (HDL) recycling in particular. TD is linked with a mutation of the ABCA1 gene codifying for the transport protein ABCA1 which, in normal conditions, enables the efflux of cholesterol through the cell membrane to HDL and apolipoprotein A1. As such, early cardiovascular events and neuropathy are common in these patients, mostly in homozygous carriers. Here, we describe the unique case of a homozygous TD patient whose diagnosis was made in later life. He was affected by the A1046D protein mutation and suffered from mild neurological symptoms and asymptomatic atherosclerosis.

Keywords: hypoalphalipoproteinemia; atherosclerosis; cardiovascular disease; HDL cholesterol; Tangier disease

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1. Introduction

Tangier disease (TD) is an extremely rare autosomal recessive disorder leading to deeply reduced high-density lipoprotein (HDL) cholesterol (HDL-C) and apolipoprotein A1 (ApoA1, the main HDL apolipoprotein) levels [1]. In this condition of pathological hypoalphalipoproteinemia, described in 117 patients across the world, HDL levels are below 20 mg/dL [2]. The illness prevalence has been estimated as $<1:10^6$ [3]. TD is related to defects of the ATP-binding cassette A1 (ABCA1) protein, a transporter of lipids across the cellular membrane [4]. ABCA1 binds to adenosine triphosphate and allows cholesterol and phospholipid efflux to ApoA1 and HDL [5]. The genetic mechanism underlying TD was recognized by the detection of the gene codifying for ABCA1 and its related variants [6]. Many mutations involving the ABCA1 gene have been found to be responsible for the homozygous form of the disease [7,8].

ABCA1 is expressed in different tissues, including the reticuloendothelial system in the liver and brain. The main consequence of TD is the lack of transport of cholesterol by HDL to the liver. As such, cholesterol accumulates inside foam cells in many organs [9]. TD patients present with a variety of signs and symptoms, such as premature atherosclerosis and early-onset cardiovascular disease, neuropathy, hepatomegaly, splenomegaly, and clouding of the cornea. Tonsils are often visibly affected by the disease as well as they frequently appear orange or yellow and are extremely enlarged. Although symptoms are

often detectable since childhood, the clinical onset varies a lot and patients are commonly diagnosed in mid-adult life.

Here, we report the unique case of a patient with homozygous TD who was diagnosed later in life, in spite of very early signs of the disease since childhood. Informed written consent to publish this case report has been obtained from the patient.

2. Case Report

The patient, a 72-year-old male, attended the Lipid Clinic at the Città della Salute e della Scienza in Turin (Italy) to ascertain the cause of previously detected low blood levels of total cholesterol, HDL, and ApoA1. He was born from consanguineous parents, namely first-degree cousins, coming from the South of Italy (Puglia). Three of his four brothers died early in infancy, but no diagnosis was made at the time, while another one was alive. His parents and grandparents passed away when they were older than seventy. He had a background of facial palsy since the age of three, hypoacusia since the age of sixty, as well as polyarthralgia, osteoarthrosis, and vertebral spine fracture. Again, hepato-splenomegaly had been recognized a few months earlier. At the time of his first examination at our Lipid Clinic, his physical presentation ruled out any further clinical signs, including tonsil involvement.

The results of the patient's lipid profile from his blood test confirmed total cholesterol levels of 46 mg/dL, HDL levels of 5 mg/dL, triglyceride levels of 97 mg/dL, and ApoA1 levels of <5 mg/dL. The low-density lipoprotein cholesterol (LDL) level, calculated by the Fredrickson formula, was 22 mg/dL. Hematocrit showed normal white and red cell counts, while platelet count was 66.000 micro L^{-1}. Apolipoprotein E phenotype was E3/E3. Owing to the presence of thrombocytopenia and splenomegaly, bone marrow biopsy was performed. It confirmed blood test data about white and red cell counts. In addition, aggregation of histiocytes and cytoplasm lipid infarction were detected. These results suggested a defect in HDL recycle; therefore, molecular analysis was set up and DNA extraction performed on blood lymphocytes.

The molecular analysis of the ABCA1 gene was firstly applied to the promoter, 50 exons, and slice junctions which were sequenced as already reported [10]. An ABCA1 mutation was detected on exon 22. A C>A change was detected at position 3137 (c.3137C>A) causing amino acid substitution Ala1046Asp (p.A1046D). This missense mutation was present on both alleles and confirmed the diagnosis of TD. Functional tests were then performed on fibroblasts to detect the effect of stimulation of the ABCA1 gene by 22-hydroxy cholesterol and 9-cis-retinoic acids. The ABCA1 protein expression on the fibroblast membrane was 20% of that of the controls, and plasma membrane enrichment of cholesterol was significant. Despite this partially preserved functionality, the membrane cholesterol efflux was absent. These laboratory methods and results were previously published and validated [11]. To improve the clinical characterization of the patient, further tests were carried out. On ophthalmological examination, mild lagophthalmos related to facial nerve VII paresis was detected, whilst pupillary mobility was normal. The cornea and retina were intact. Bilateral cataracts and narrow vessels in the fundus of the eye were detected as well. Bilateral mixed sensory and conductive hearing loss were detected on audiometry. Electromyography applied to the median, ulnar, perineal, and sural nerves of the lower limbs identified bilateral peripheral sensitive neuropathy. Abdominal ultrasonography confirmed mild hepatomegaly and splenomegaly. The abdominal aorta had atherosclerotic plaques with no blood flow obstruction. In addition, a cardiovascular examination was carried out. Carotid artery ultrasounds detected a mean intimal media thickness of 0.8 mm in line with age (age- and gender-related reference value: 0.9 mm), but there were no atherosclerotic plaques. Echocardiography showed concentric left ventricular hypertrophy. Cardiac contractile function was preserved (ejection fraction 62%, with no wall motion abnormalities). The left atrium and right chambers were enlarged. The mitral and aortic valves were calcified, leading to mild and moderate regurgitation, respectively. The tricuspid valve was regurgitant as well, with mild-to-moderate pulmonary hypertension

(mean PAPS 35 mmHg). Dobutamine stress echocardiography, with an increasing dose from 10 mcg/kg/min to 40 mcg/kg/min, displayed reversible inducible ischemia. During the test, the patient was asymptomatic in terms of chest pain or shortness of breath. Blood pressure increase during the test was within the normal range.

3. Discussion

TD occurs early in the first decade of life with tonsil enlargement and corneal clouding. Neuropathy and cardiovascular diseases are its most harmful after-effects [12]. Heterozygous TD carriers have relatively low HDL levels and cholesterol esters do not accumulate in their body organs. Conversely, homozygous carriers who inherited both recessive genes have extremely low HDL levels and cholesterol esters are stored in their organs [13].

The main findings in Tangier disease are reported in Table 1.

Table 1. Main clinical findings in Tangier disease [14,15].

Lipid profile	Severe deficiency or absence of HDL-C and apo A-I, decreased total cholesterol and LDL-C, mild-to-moderate hypertriglyceridemia
Oral cavity	Enlarged yellow/orange tonsils
Cardiovascular system	Premature atherosclerosis, coronary artery diseases, strokes, heart valve involvement
Nervous system	Peripheral neuropathy: syringomyelia-like neuropathy, multifocal sensorial and motor neuropathy, distal symmetric polyneuropathy, facial diplegia. SNC involvement: multiple sclerosis-like neurologic presentation (one case), with optic neuritis, internuclear ophthalmoplegia, ocular palsies, dysarthria and gait problems
Reticuloendothelial system	Hepatomegaly, splenomegaly, lymphadenopathy
Ocular system	Clouding of the cornea, ectropion
Hematologic manifestations	Thrombocytopenia, reticulocytosis, hemolytic anemia, stomatocytosis
Skin/nail involvement	Dry skin, skin lesions (prurigo nodularis, skin ulcer, painless scalds, burn scars), nail dystrophy
Others	Abdominal pain, diabetes, hearing loss

The prevalence varies in the previous reports published: Muratsu et al. [16], in their review in 2016, focused on cardiovascular diseases and reported that angina was observed in 24.8% of cases and other vascular diseases in 21.8%; Mercan et al. [15], in their 2018 review on TD with peripheral neuropathy, found that the clinical findings with the highest prevalence were splenomegaly (40.7%), orange-yellow oropharyngeal lymphoid tissues (33.3%), thrombocytopenia (27.8%), tonsillectomy history (24%), corneal opacity (22.2%), coronary artery diseases (14.8%), and skin lesions (14.8%); and Assmann et al. [1], in 1995, reported tonsillar enlargement in 67%, neuropathy in 56%, splenomegaly in 59%, hepatomegaly in 38%, and corneal opacification in 24%.

In the present paper, we underline the clinical presentation and extremely delayed TD diagnosis in an elderly homozygous patient, although he suffered peripheral neuropathy from the pediatric age. Recent papers have acknowledged late TD diagnosis but patients were recognized in their fifties; our patient is then, at present, the oldest one, as far as we know [2,4]. In this respect, two points need to be highlighted.

Firstly, premature atherosclerosis is one of the hallmarks of the disease. This point is consistent with the huge disease-associated pathological reduction in HDL [17]. More than 30% of TD patients suffer from early adverse cardiovascular events [16] and extensive coronary calcifications have been demonstrated by intravascular ultrasound (IVUS) even in asymptomatic patients [18]. However, the patient described here had never suffered

from myocardial infarction or stroke, and just a silent ischemia was detected by pharmacological stress echocardiography. This is consistent with previous reports as the role of cardiovascular disease in TD is still under debate [19,20]. The patient showed other typical signs of TD including peripheral neuropathy, thrombocytopenia, and hepato-splenomegaly. Surprisingly, the tonsils, cornea, and lymph nodes were not involved, notwithstanding the expected accumulation of cholesterol into the reticuloendothelial cells in these organs as well. Cholesterol accumulation was present in the patient's liver and spleen and responsible for their enlargement. This clinical presentation was quite unusual but in line with the phenotypic variability of the disorder [21]. Other atypical or even unique symptoms have also been described such as spleen bleeding [22], central nervous system disorders including intermittent ophthalmoplegia, optic neuritis, ocular palsies, and gait disorders [21]. A previous case where symptoms were totally lacking was described as well [23].

Secondly, the diagnosis of TD is often challenging as the related signs and symptoms could be attributed to more common conditions. Our patient suffered from facial palsy since childhood, and hypoacusia and from lagophthalmos later on in life. These symptoms were consistent with facial nerve VII involvement, but nobody has thought that they could be linked with TD. The latter was first suspected because of the bone marrow lipid accumulation detected by means of biopsy. The extreme reduction in HDL and ApoA1 levels, both lower than 5 mg/dL, combined with hepato-splenomegaly and neurological symptoms, as well the consanguinity, were other elements of suspicion. In fact, TD should be suspected when two clinical symptoms are associated with two biochemical abnormalities. The detection of the homozygous variant A1046D confirmed the TD diagnosis [24]. This variant is reported in the ENSEMBL database, with an extremely low frequency (two Europeans out of more than 250 thousand genomes), and bioinformatics predictors (e.g., mutation assessor) classify it as pathogenic/probably pathogenic. The mutation was previously described in two patients suffering from Tangier disease: in the first case, the patient had a homozygous status in which ABCA1-mediated cholesterol efflux resulted in the abolishment of fibroblasts; in the second case, this occurred in association with Y1532C (c.4595A>G) in exon 34, and W1699C (c.5097G>T) in exon 37 [11,25]. HDL in the latter proband was indetectable and pCAD was present. The present variant p.A1046D is located at the intracellular domain of the ABCA1 gene and is demonstrated to impact on the three-dimensional folding of ABCA1. This mechanism characterizes the extracellular mutations that exert a heavy impact on the membrane. These latter variants destroy the domain interacting with the extracellular loops, then abolish the binding to ApoA1. The result in both conditions is the impaired transfer capacity of cholesterol efflux then a complete loss of function. This is a critical point as the present variant can reach the plasma membrane, it binds ApoA1, and it shows a residual capacity without any folding effects.

Additional functional aspects of this variant are reported in vitro [26]. Cholesterol efflux function was significantly impaired. This explains the reduction in ApoA1 and HDL levels and the related atherogenicity [26]. Of note, the concomitant very low LDL levels observed in our patient could explain the slow progress of atherosclerotic coronary disease. We did not determine small dense LDL in the patient and the role of these particles in TD is unclear; despite overproduction of VLDL, the reduction in LDL observed in TD is due to enhanced catabolism, secondary to changes in LDL composition and size [27].

When hypoalphalipoproteinemia occurs, the differential diagnosis is mandatory and includes primary and secondary defects. The former encompasses lecithin–cholesterol acyltransferase (L-CAT) deficiency and ApoA1 deficiency. However, their typical symptoms (proteinuria and renal damage in L-CAT and xanthoma in ApoA1 deficiency) were lacking in our patient. The latter includes diabetes and use of some medications [14].

Owing to the lack of a specific therapy (old and new drugs known to increase HDL levels are ineffective in this setting [14]), a tight follow-up was established. To improve symptoms, salicylic acid and beta blockers were administered to the patient because of his cardiac involvement. The therapeutic approach in TD patients should also be addressed to reduce the cardiovascular risk then to improve lifestyle and glycemic and

blood pressure control. Furthermore, lipid-lowering drugs, including fibrates or statins, need consideration if hypertriglyceridemia occurs or when non-HDL > 70 mg/dL. The efficacy of glycosphingolipid synthesis inhibitors has been postulated, opening a window to the possibility of their future use in the treatment of TD neuropathy. These drugs, already tested in preliminary trials, have shown interesting results in Niemann–Pick type C and counteract lysosomal lipid storage, as shown in TD, suggesting their potential use as treatment for TD peripheral neuropathy [28].

4. Conclusions

In conclusion, this patient's case highlights the importance of taking into account even mild symptoms as well as checking lipid panels since childhood to rule out any primary disorders, TD included [29]. To reach this goal, the awareness of physicians and healthcare workers in general should be improved. The reported delayed presentation in a homozygous TD subject is unique.

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References

1. Assmann, G.; von Eckardstein, A.; Brewer, H.B. Familial high density lipoprotein deficiency: Tangier disease. In *The Metabolic and Molecular Basis of Inherited Disease*, 7th ed.; Scriver, C.R., Beaudet, A.L., Sly, W.S., Valle, D., Eds.; McGraw-Hill: New York, NY, USA, 1995; pp. 2053–2072.
2. Wong, C.L.; Hung, L.Y.; Siu, W.K.C.; Tam, V.H.K.; Mak, C.M. A novel splicing variant in ABCA1 in the first reported Hong Kong Chinese patient with high-density lipoprotein deficiency. *Endocrinol. Diabetes Metab. Case Rep.* **2024**, *2024*, 23-0102. [CrossRef] [PubMed]
3. Orphanet. Tangier Disease—ORPHA:31150. Available online: https://www.orpha.net/en/disease/detail/31150 (accessed on 1 October 2024).
4. Barbosa-Gouveia, S.; Fernández-Crespo, S.; Lazaré-Iglesias, H.; González-Quintela, A.; Vázquez-Agra, N.; Hermida-Ameijeiras, Á. Association of a Novel Homozygous Variant in ABCA1 Gene with Tangier Disease. *J. Clin. Med.* **2023**, *12*, 2596. [CrossRef]
5. Francis, G.A.; Knopp, R.H.; Oram, J.F. Defective removal of cellular cholesterol and phospholipids by apolipoprotein A-I in Tangier disease. *J. Clin. Investig.* **1995**, *96*, 78–87. [CrossRef] [PubMed]
6. Marcil, M.; Brooks-Wilson, A.; Clee, S.M.; Roomp, K.; Zhang, L.H.; Yu, L.; Collins, J.A.; van Dam, M.; Molhuizen, H.O.; Loubster, O.; et al. Mutations in the ABC1 gene in familial HDL deficiency with defective cholesterol efflux. *Lancet* **1999**, *354*, 1341–1346. [CrossRef] [PubMed]
7. Brooks-Wilson, A.; Marcil, M.; Clee, S.M.; Zhang, L.H.; Roomp, K.; van Dam, M.; Yu, L.; Brewer, C.; Collins, J.A.; Molhuizen, H.O.; et al. Mutations in ABC1 in Tangier disease and familial highdensity lipoprotein deficiency. *Nat. Genet.* **1999**, *22*, 336–345. [CrossRef] [PubMed]
8. Rust, S.; Rosier, M.; Funke, H.; Real, J.; Amoura, Z.; Piette, J.C.; Deleuze, J.F.; Brewer, H.B.; Duverger, N.; Denèfle, P.; et al. Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nat. Genet.* **1999**, *22*, 352–355. [CrossRef]
9. Hara, H.; Yokoyama, S. Interaction of free apolipoproteins with macrophages. Formation of high-density lipoprotein-like lipoproteins and reduction of cellular cholesterol. *J. Biol. Chem.* **1991**, *266*, 3080–3086. [CrossRef]
10. Pisciotta, L.; Hamilton-Craig, I.; Tarugi, P.; Bellocchio, A.; Fasano, T.; Alessandrini, P.; Bon, G.B.; Siepi, D.; Mannarino, E.; Cattin, L.; et al. Familial HDL deficiency due to ABCA1 gene mutations with or without other genetic lipoprotein disorders. *Atherosclerosis* **2004**, *172*, 329–340. [CrossRef]
11. Pisciotta, L.; Bocchi, L.; Candini, C.; Sallo, R.; Zanotti, I.; Fasano, T.; Chakrapani, A.; Bates, T.; Bonardi, R.; Cantafora, A.; et al. Severe HDL deficiency due to novel defects in the ABCA1 transporter. *J. Intern. Med.* **2009**, *265*, 359–372. [CrossRef]
12. Kolovou, G.D.; Mikhailidis, D.P.; Anagnostopoulou, K.K.; Daskalopoulou, S.S.; Cokkinos, D.V. Tangier disease four decades of research: A reflection of the importance of HDL. *Curr. Med. Chem.* **2006**, *13*, 771–782. [CrossRef]

13. von Eckardstein, A. Differential diagnosis of familial high density lipoprotein deficiency syndromes. *Atherosclerosis* **2006**, *186*, 231–239. [CrossRef] [PubMed]
14. Alshaikhli, A.; Vaqar, S. Tangier Disease. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024; [Updated 8 May 2023]. Available online: https://www.ncbi.nlm.nih.gov/books/NBK562250/ (accessed on 1 October 2024).
15. Mercan, M.; Yayla, V.; Altinay, S.; Seyhan, S. Peripheral neuropathy in Tangier disease: A literature review and assessment. *J. Peripher. Nerv. Syst.* **2018**, *23*, 88–98. [CrossRef] [PubMed]
16. Muratsu, J.; Koseki, M.; Masuda, D.; Yasuga, Y.; Tomoyama, S.; Ataka, K.; Yagi, Y.; Nakagawa, A.; Hamada, H.; Fujita, S.; et al. Accelerated atherogenicity in Tangier disease. *J. Atheroscler. Thromb.* **2018**, *25*, 1076–1085. [CrossRef] [PubMed]
17. Asztalos, B.; Roheim, P.S. Presence and formation of 'Free Apolipoprotein A-I-like' particles in human plasma. *Arterioscler. Thromb.* **1995**, *15*, 1419–1423. [CrossRef] [PubMed]
18. Komuro, R.; Yamashita, S.; Sumitsuji, S.; Hirano, K.; Maruyama, T.; Nishida, M.; Matsuura, F.; Matsuyama, A.; Sugimoto, T.; Ouchi, N.; et al. Tangier disease with continuous massive and longitudinal diffuse calcification in the coronary arteries: Demonstration by the sagittal images of intravascular ultrasonography. *Circulation* **2000**, *101*, 2446–2448. [CrossRef] [PubMed]
19. Asztalos, B.F.; Brousseau, M.E.; McNamara, J.R.; Horvath, K.V.; Roheim, P.S.; Schaefer, E.J. Subpopulations of high density lipoproteins in homozy- gous and heterozygous Tangier disease. *Atherosclerosis* **2001**, *156*, 217–225. [CrossRef]
20. Brunham, L.R.; Singaraja, R.R.; Hayden, M.R. Variations on a gene: Rare and common variants in ABCA1 and their impact on HDL cholesterol levels and atherosclerosis. *Ann. Rev. Nutr.* **2006**, *26*, 105–129. [CrossRef]
21. Smita, I.; Brautbar, A.; Virani, S.S.; Anand, A.; Polisecki, E.; Asztalos, B.F.; Ballantyne, C.M.; Schaefer, E.J.; Jones, P.H. A novel mutation in the ABCA1 gene causing an atypical phenotype of Tangier disease. *J. Clin. Lipidol.* **2013**, *7*, 82–87.
22. Maranghi, M.; Truglio, G.; Gallo, A.; Grieco, E.; Verrienti, A.; Montali, A.; Gallo, P.; Alesini, F.; Arca, M.; Lucarelli, M. A novel splicing mutation in the ABCA1 gene, causing Tangier disease and familial HDL deficiency in a large family. *Biochem. Biophys. Res. Commun.* **2019**, *508*, 487–493. [CrossRef]
23. Gell, J.; Heyningen, C. Homozygous Tangier disease with undetectable serum high density lipoprotein cholesterol levels and no clinical features. *OA Case. Rep.* **2013**, *2*, 126.
24. Koseki, M.; Yamashita, S.; Ogura, M.; Ishigaki, Y.; Ono, K.; Tsukamoto, K.; Hori, M.; Matsuki, K.; Yokoyama, S.; Harada-Shiba, M. Current Diagnosis and Management of Tangier Disease. *J. Atheroscler. Thromb.* **2021**, *28*, 802–810. [CrossRef] [PubMed]
25. Pervaiz, M.A.; Gau, G.; Jaffe, A.S.; Saenger, A.K.; Baudhuin, L.; Ellison, J. A Non-classical Presentation of Tangier Disease with Three ABCA1 Mutations. *JIMD Rep.* **2012**, *4*, 109–111. [PubMed]
26. Singaraija, R.R.; Visscher, H.; James, E.; Chroni, A.; Coutinho, J.M.; Brunham, L.R.; Kang, M.H.; Zannis, V.I.; Chimini, G.; Hayden, M.R. Specific Mutations in ABCA1 Have Discrete Effects on ABCA1 Function and Lipid Phenotypes Both In Vivo and In Vitro. *Circ. Res.* **2006**, *99*, 389–397. [CrossRef] [PubMed]
27. Schaefer, E.J.; Anthanont, P.; Diffenderfer, M.R.; Polisecki, E.; Asztalos, B.F. Diagnosis and treatment of high density lipoprotein deficiency. *Prog. Cardiovasc. Dis.* **2016**, *59*, 97–106. [CrossRef]
28. Hooper, A.J.; Hegele, R.A.; Burnett, J.R. Tangier disease: Update for 2020. *Curr. Opin. Lipidol.* **2020**, *31*, 80–84. [CrossRef]
29. Martino, F.; Bassareo, P.P.; Martino, E.; Romeo, F.; Calcaterra, G.; Perrone Filardi, P.; Indolfi, C.; Nodari, S.; Montemurro, V.; Guccione, P.; et al. Cardiovascular prevention in childhood: A consensus document of the Italian Society of Cardiology Working Group on Congenital Heart Disease and Cardiovascular Prevention in Paediatric Age. *J. Cardiovasc. Med.* **2023**, *24*, 492–505. [CrossRef]