Large Inflammatory Pericardial Effusion and Macrocytic Anemia in a Vogt-Koyanagi-Harada Patient

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Abstract

Vogt-Koyanagi-Harada (VKH) disease is a multisystemic autoimmune disease which targets pigmented tissues, especially the eyes, in a genetically susceptible individual (HLA-DR4 carrier). It is characterized by a bilateral, vision-threatening uveitis that evolves in 4 phases and by extracocular manifestations in other tissues containing melanin.

We report an association of complete VKH disease, vitamin B-deficient macrocytic anemia and a large, circumferential pericardial effusion in an 82-year old woman.

Although there is no known report, to the best of our knowledge, of cardiac manifestations in VKH disease, we argue that the inflammatory pericardial effusion we found is a cardiac manifestation of VKH disease since this disease is directed against melanin cells which can be found in the heart, and because we ruled out other common causes of pericardial effusion such as tuberculosis and neoplasm. Since genetic susceptibility to autoimmune diseases is a fertile environment for the development of auto-immune diseases, which frequently coexist, we suggest that our patient presents pernicious anemia associated with VKH disease.

In the light of the above observations, we suggest a systematic screening of VKH patients (Electrocardiogram, transthoracic echocardiography) for possible, potentially lethal cardiac manifestations before beginning VKH therapy.

Keywords: Vogt-Koyanagi-Harada disease; Uveitis, HLA-DR4; Pericardial effusion; Megaloblastic anemia, Vitamin B deficiency; Melanin

Abbreviations: VKH: Vogt-Koyanagi-Harada; EKG: Electrocardiogram; TTE: Transthoracic Echocardiography

Introduction

The prevalence of auto-immune diseases is increasing, with accompanying medical and socio-economic impact [1]. Individuals susceptible to autoimmune diseases sometimes suffer from an association of autoimmune diseases.

We report an association of large, inflammatory pericardial effusion and macrocytic vitamin-deficiency pancytopenia in an 82-year old VKH patient; which to the best of our knowledge is the first of its kind.

Case Presentation

An 82-year old nearly blind and deaf patient presented with a 4-year history of grade II dyspnea, which progressed to grade III in the past 15 days, without any other notable cardiovascular symptom. Inquiry into her medical history noted splenectomy 20 years ago and a notion of anemia with no adherence to an undocumented prescribed treatment. She also presented complaints of bilateral visual loss starting about 15 years ago in the absence of trauma or surgery, later complicated with cataract in the left eye, progressive bilateral depigmentation starting about 10 years ago, and progressive bilateral hearing loss noted about 5 years ago. She was also on oral medication for arterial hypertension about 2-years ago.

General medical examination noted apyrexia, a thin patient (36 kg/ 155 cm), blood pressure of 122/58 mmHg, heart rate 110 beats per minute, respiratory rate 27 cycles per minute. Cardiovascular inspection noted spontaneously turgent jugular veins and no oedema. Apical beat was hyper pulsatile and peripheral pulse was symmetrically present. Auscultation noted irregular heartbeats, systolic murmur in the tricuspid area, splitting of the second heart sound with loud pulmonary valve closure sound in the pulmonary area. Pulmonary auscultation noted crepitation in lower third of both lung fields. Electrocardiogram noted atrial fibrillation with an irregular ventricular rate at 90 beats per minute, normal axis, microvoltage in peripheral leads and Q-wave couples with incomplete left bundle branch block in anteroseptal leads.

Transthoracic echocardiography showed a large circumferential pericardial effusion measuring 15 mm at the lateral region of the right ventricle and 25-27 mm at the lateral region of the left ventricle. There was no hemodynamic consequence due to the effusion: both ventricles were neither dilated nor dysfunctional, no significant variation in mitral or tricuspid inflow. Inferior vena cava measured 20 mm. There was mild left ventricular hypertrophy, moderate bialateral enlargement, severe tricuspid regurgitation and severe pulmonary hypertension estimated at 86 mmHg (Figure 1).

Dermatological examination noted the presence of poorly demarcated depigmented patches involving both sides of the body in a symmetric distribution, in favour of generalized non-segmental vitiligo [2] (Figure 2).

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Ophthalmological examination noted bilateral reduction in visual acuity below 1/60: hand movement for left eye and count fingers for right eye. Slit-lamp examination was notable for corneal dystrophy in the left eye, impeding fundoscopy examination (Figure 3); whilst the right eye showed clear cornea, no inflammation and posterior synchia with impossibility of complete dilation despite repeated doses of mydriatic eye drops. Fundoscopic examination of the right eye revealed depigmentation of the posterior segment (sunset glow fundus), optic atrophy, thin blood vessels in favour of VKH sequelae (Figure 4). Audiometry noted advanced bilateral hearing loss.

Full blood count noted macrocytic anaemia (hemoglobin (Hb) concentration: 5.6 g/dL, mean cellular volume: 146.9 μ³, mean cell Hb: 48.3pg), thrombopenia (platelet count at 31000/mm³, with platelet aggregates and macro platelets), leukopenia at 2600/mm³, anisochromia and anisopoikilocytosis.

Vitamins B9 level was 8.37 ng/ml (NV: 5.6-45.8) and vitamin B12 level was 225 pg/mL (normal value (NV): 191-663 pg/mL) after transfusing 4 units of packed red blood cells. Myelogram noted vitamin-deficiency dysmyelopoiesis: megakaryocytes (+), important granulocyte dysmorphism with giant metamyelocytes, asynchrony in nucleo-cytoplasmic maturation of red blood cells and the presence of few siderocytes and no ringed sideroblast. Gastric parietal cell antibody test was negative. HLA analysis was positive for HLA-DRBI 0413 and HLA DQB1 0306. Thyroid gland test were normal.

Patient underwent surgical draining of the pleural effusion and pericardial biopsy. 500 mL of serofibrinous fluid was collected. Biochemical analysis of pleural liquid was in favour of an exudate: Rivalta +, LDH: 1640 u/l/ml, proteins: 51 g/L (serum proteins=72 g/L, giving a ratio of 0.71). Cytobacteriological testing of pleural fluid noted mild leucocytic reaction, no malignant cell, and no germ was identified after 48-hour culture. Detection of Mycobacterium tuberculosis in pericardial liquid by real-time PCR (Xpert MTB-RIF Assay G4) was negative. Anatomopathological examination of pericardium fragments showed discrete nonspecific chronic inflammatory changes, and no sign of malignancy.

Patient was put on an intramuscular hydroxocobalamin regimen: 5000 μg (one injection) per day for 10 days, then one injection per week for one month, then one injection per month for life. Full blood count test 2 weeks into treatment showed remarkable improvement: hemoglobin at 9.3 g/100 mL, mean cellular volume was 97.3 μ³, mean cellular hemoglobin was 33.9 pg, platelet count was 313000/mm³, and leucocyte count was at 3 500/mm³.

Discussion

Vogt-Koyanagi-Harada (VKH) disease is a multisystem autoimmune disease which targets tissues containing melanin. It is characterized by a bilateral, vision-threatening uveitis that evolves in 4 stages (prodromal, acute uveitis, chronic convalescent and chronic recurrent), and is frequently associated with neurological, auditory and integumentary manifestations [3]. Its’ global incidence is uneven: very frequent in the Asian, Hispanic, American Indian, Mediterranean and middle eastern populations and rarely seen in Caucasians in Europe and in black people in Africa [3,4]. VKH disease predominantly affects adults aged 20-50, but also affects children and elderly people. VKH disease reportedly affects more females than males, probably due to the influence of sex hormones such as estrogen and progesterone [3].

Diagnosis of VKH disease is primarily clinical, according to the 2001 Revised Diagnostic Criteria, which divides the disease into three categories: complete, incomplete and probable [3,4]. Ancillary tests including fluorescein angiography, ultrasonography, indocyanine green angiography, optical coherence tomography, lumbar puncture are useful for diagnosis of incomplete forms or early stages, for monitoring the efficacy of treatment, detection of complications and for research purposes.

VKH disease is the result of an exaggerated HLA-DRBI/T-cell auto-immune response of a sensitized individual towards autoantigens (such as melanocyte-related antigens) or exogenous peptides simulating the autoantigens (such as CMV antigens), unsuppressed by natural regulatory T-cells. Important factors in the development of VKH disease include genetic susceptibility (presence of genes coding
for HLA-DR4 antigens and other predisposing genes such as certain killer immunoglobulin-like receptor (KIR) genes and probably environmental factors such as infections due to Epstein-Barr and Cytomegalovirus [3].

Melanocytes derive from neural crest-derived precursors known as melanoblasts. Neural crest cells are pluripotent cells that arise from the dorsal aspect of the neural tube between the surface ectoderm and the neural plate. They give rise to neurons and glia of the peripheral sensory and autonomic nervous system, neuroendocrine cells, craniofacial mesenchyme that forms bones and cartilage of the head, and cardiac cells [2,5]. Melanoblasts migrate along a dorsolateral pathway beneath the ectoderm and in so doing invade and colonize skin and hair follicles, and along the ventral pathway, giving rise to melanocyte populations that exist in the eye, inner ear, heart and leptomeninges of the brain [5]. Melanocytes provide photo protection by producing melanin, predominantly in the melanosome. Acquired, progressive loss of melanocytes which manifests as white macules on the skin, mucosa or hair is termed vitiligo.

VKH is an auto-immune disease comprising vitiligo and generalized vitiligo is known to be associated with other auto-immune disease such as autoimmune thyroid disease, rheumatoid arthritis, adult onset type 1 diabetes mellitus, systemic lupus erythematosus and pernicious anemia. Anti-parietal cell antibody (APCA) targeting the gastric proton pump – the H+/K+/ ATPase can be found in 85-90% of patients with pernicious anemia, in 15% of vitiligo patients, in up to 20-30% of patients suffering from auto-immune thyroid diseases such as Hashimoto or Graves-Basedow disease, in coeliac disease patients and in type 1 Diabetes patients [1]. ACPA are a sensitive but nonspecific screening tool for auto-immune gastritis and pernicious anemia, a type of megaloblastic anemia.

Megaloblastic or macrocytic anemia results from asynchrony in nuclear-cytoplasmic maturation owing to stagnant, ineffective DNA synthesis, resulting in large cells with immature nuclei, anemia and cytopenias. Vitamin B12 and folate deficiencies are the most important causes of megaloblastic anemia. Other causes of megaloblastic anemia include drugs such as antibiotics, inborn errors of metabolism, acute megaloblastic anemia due to nitrous oxide exposure or acute illness, idiopathic causes and thiamine-responsive megaloblastic anemia [6].

Folate deficiencies can be due to decreased intake (nutritional deficiency especially in the elderly, alcoholics or in poverty), decreased absorption or increased demand, whilst cobalamin deficiencies are often due to impaired absorption (pernicious anemia) or decreased intake (vegans and vegetarians) [6]. Absolute vitamin B12 deficiency affects up to 6% of those aged 60 years and older, whereas marginal deficiency occur in close to 20% of patients in later life [7].

The main clinical features of vitamin B12 deficiency include anemias, cytopenias, and glossitis, and cardiomyopathy, yellow coloration of the skin, weight loss, autoimmune defects, and cerebral manifestations including mental confusion, paranoia, dementia and psychosis [6]. About 10% of vitamin B12 deficient patients show hyperpigmentation and some patients with pernicious anemia have associated autoimmune vitiligo. With an aging population, screening for vitamin B12 level as part of anemia and cognitive impairment workup is more common. Clinical manifestations of folate-deficient megaloblastic anemia include a history of nutritional deficiency with no neurologic signs, and response to folate therapy.

Megaloblastic anemia presents on blood count and examination of blood smear as anemia with increased cell indices, anisocytosis, poikilocytosis and hypersegmented neutrophils. B12 level of less than 200 pg/mL suggests deficiency, but also low or absent haptocorrnin, the major plasma B12 binding protein [6]. Megaloblastic anemias are usually associated with considerable extravascular hemolysis, thereby increasing serum bilirubin and lactate deshydrogenase levels. Folate deficiency is suggested by plasma or serum levels of less than 4µg/mL or a borderline value of 4-8 µg/mL associated with high plasma levels of homocysteine.

Impaired vitamin B12 absorption is primarily caused by pernicious, an autoimmune disease that affects the gastric parietal cells. Destruction of these cells curtails the production of intrinsic factor and subsequently limits vitamin B12 absorption. Laboratory evidence of parietal cell antibodies is approximately 85 to 90 percent sensitive for the diagnosis of pernicious anemia. However, the presence of parietal cell antibodies is nonspecific and occurs in other autoimmune states. Intrinsic factor antibody is only 50 percent sensitive, but it is far more specific for the diagnosis of pernicious anemia.

Our patient presented a complete form of HLA-DRB1*0413 and HLA DQB1*0306 positive VKH disease associated with macrocytic anemia and a large circumferential pericardial effusion [8].

In light of the auto-immune context: VKH directed against melanocyte cells which can be found in the heart, in the absence of other major causes particularly tuberculosis and neoplasm, and in the presence of an inflammatory aspect noted in pleural fluid and on anatomopathological analysis of pericardium fragments, we argue that our patient’s inflammatory pericarditis could be linked to VKH disease. Cardiac involvement in VKH disease has never been reported in literature probably due to the fact that this disease is often diagnosed and followed up by ophthalmologists. Furthermore, corticoid and immunosuppressive treatment of VKH patients silence possible cardiac inflammations. The Q wave noticed on anteroseptal leads could also be in favour with coronary manifestations of VKH disease, since many auto-immune diseases are known to be have coronary complications [8-10].

The vitamin-deficiency macrocytic anemia could be due to dietary deficiency but also due to pernicious anemia. ACPA are 85-90% sensitive, thus do not rule out this eventuality. We argue that this case of VKH disease is probably associated with pernicious anemia, based on the auto-immune context and literature evidence in favour of associations between generalized vitiligo and pernicious anemia [2,6].

Conclusion
VKH disease is indeed a multisystemic, pluridisciplinary entity. Visual and auditory prognosis becomes of less importance when confronted with cardiac manifestations that could engage vital prognosis in the absence of appropriate management. We suggest routine screening of VKH patients by electrocardiogram and transthoracic echocardiography before beginning VKH treatment

Disclosure
The authors report no conflict of interest in this work.

References


