WILD syndrome: A rare presentation of primary lymphedema, generalized warts and immune deficiency diagnosed in Bangladesh

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Abstract

WILD syndrome is a rare disease characterized by warts, impaired cell mediated immunity, primary lymphedema and anogenital dysplasia. Our patient who is a 13 year old boy presented with swelling of right lower limb since birth. The swelling gradually involved both upper limbs and right side of his face. The swelling over the right lower limb grew to such an extent that he has been unable to do his daily activities for the last 3 years and warty skin lesions over his whole body for the last 5 years. At the same time he has swelling of his external genitalia and warty lesion around the anus. He has recurrent painless swelling of his abdomen with scanty micturition. On examination, he was mildly anemic, non-icteric, non-pitting edema of right leg, normal vital parameters, right sided pleural effusion, pericardial effusion and ascites, no organomegaly. Swelling and distortion of right lower limb with nodular lesions over the right leg, generalized hyper and hypopigmented verrucous papules and paques over whole body, swelling of the glans and flat warts around the anus. His investigations revealed leucopenia, chylous pleural effusion, lymphedema of right lower limb with venous incompetency and normal arterial supply, reduced CD4 and CD8 T cell count, normal immunoglobulin levels, negative ICT for filarial, histology of skin lesion revealed elephantiasis verrucosa nostra, and anogenital dysplasia with a large number of koilocytes.

Key words

Generalized warts, primary lymphedema, impaired cell mediated immunity, anogenital dysplasia, koilocytes.

Introduction

WILD syndrome is a rare disease characterized by generalized warts, impaired cell mediated immunity, primary lymphedema and anogenital dysplasia. A very few cases has been reported worldwide and its genetic inheritance has not been determined yet. It has features similar to GATA2 gene deficiency. The first patient with WILD syndrome was reported by Ostrow et al. thirty years back.¹

Case report

A 13-year-old boy with primary lymphedema
presented for evaluation of persistent generalized warts that appeared at the age of eight, initially affecting the right leg. He was the 5th issue of consanguineously married parents, and none of his relatives had similar findings. But his two siblings and an aunt had suspected neuromuscular disorder. Swelling of right lower limb was noticed at birth, and later progress to involve both the upper limbs and right side of his face. At the age of eight, the patient developed disseminated skin colored flat warts over the swollen right leg, gradually involving the whole body including palms, soles and perianal region along with disfigurement of his external genital organ. The swelling of the right lower limb was extensive and deformed with foul smelling discharge that had impaired his daily activities for the last several years. He had history of recurrent painless abdominal swelling with scanty micturition for the last three years which used to subside after taking oral steroid and diuretics. There was frequent passage of whitish loose stools for the same duration.

His physical examination revealed mild anemia and swelling of his right cheek, arms and forearms on both sides; hugely distended and deformed right lower limb (Figure 1). All the swellings were painless and non-pitting. There were multiple grouped skin colored painless nodules over the right leg extending from knee to dorsum of foot with foul smelling whitish discharge from the clefts of the foot (Figure 2). Both hypopigmented and hyperpigmented verrucous papules and plaques were distributed over whole body (Figure 3), with flat warts around the anus (Figure 4) and swelling of his glans.

He had pericardial and right sided pleural effusion, and ascites with no organomegally. Results of laboratory investigations revealed hemoglobin 11.5 g/dl, WBC 12,000/cmm, differential count: neutrophil 89%, lymphocyte
05%, monocyte 03%, eosinophil 03%, low serum albumin level of 1.6 gm/dl, trace of protein in urine, and fat globules in stool. Serum creatinine and SGPT were within normal reference range. ICT for filaria was negative, pleural fluid study was chylous in nature. HIV 1&2, HBsAg, anti HCV were negative. Notably decreased CD4 T cells of 138/μl (ref range 410-1590/μl) and CD8 T cells of 91/μl (ref range 150-1000/μl), but immunoglobulin levels were within reference range.

Chest X-ray revealed right-sided moderate pleural effusion and pericardial effusion. X-ray of right lower limb showed no bone deformity. Magnetic resonance arteriography (MRA) of lower limbs was normal (Figure 5). Color duplex study of right lower limb revealed incompetent long saphenous and common femoral venous valves. Lymphoscintigraphy of lower extremities showed lymphatic obstruction. Histological evaluation of nodules on this limb revealed Elephanthisis verrucosa nostra, warty lesions revealed features of HPV associated verruca vulgaris as evidenced by presence of koilocytes (Figure 6), and perianal skin lesion revealed low grade dysplasia. Due to lack of facility HPV typing could not be done in this patient.

With the features of primary lymphedema, generalized warty lesion, depressed cell mediated immunity and anogenital dysplasia, we have finally diagnosed the boy as WILD syndrome.

For improving the patient’s wellbeing, multi stage bulk reduction from the enlarged and deformed right lower limb and anastomosis of the lymphatic channel with venous system has been planned. Cryotherapy and electrosurgery will be used for removing the warts.

Discussion

GATA2 deficiency is a germline disease which causes viral and bacterial infections, cytopenias, myelodysplasia, myeloid leukemias, pulmonary alveolar proteinosis and lymphedema. It has a wide range of clinical manifestations some of
which overlap with WILD syndrome. The age of clinical presentation ranges from early childhood to late adulthood, with most occurring in adolescence to early adulthood.²

As WILD syndrome is a rare disease, we have considered a number of differentials before considering our final diagnosis.

Epidermodysplasia verruciformis is a genodermatosis where abnormal susceptibility to infection by various HPV types occurs, which normally does not occur in immunocompetent individuals. It occurs due to mutation of EVER1 and EVER2 genes. Patients usually presents with disseminated flat warts at an early age and about 30% develops skin cancer. There is no association of primary lymphedema in this syndrome.³⁴

WHIM syndrome is an acronym derived from the major features of the disorder that include warts, hypogammaglobulinemia, recurrent bacterial infection and myelokathexis (apoptosis of mature myeloid cells in the bone marrow). Here mutation occurs in chemokine receptor CXCR4.⁵

Milroy’s disease is an autosomal dominant disorder presents with unilateral or bilateral lymphedema at or soon after birth. Skin changes due to lymphatic obstruction are present, also known as elephantiasis verrucosa nostra and chylous discharge may be present. Generalized skin lesions are usually absent.⁶

Klippel-Trenauny syndrome is characterized by nevus flammeus, venous malformation and soft tissue hypertrophy of the affected extremity, in 95% cases affecting the lower extremity. The most common and earliest sign is nevus flammeus, usually confined to one extremity, and the involved limb is larger and longer than the other. Generalized skin lesions are usually absent.⁷

WILD syndrome is characterized by generalized warts, depressed cell mediated immunity, primary lymphedema and anogenital dysplasia. Patients usually present with primary lymphedema at or soon after birth which may affect single limb or both limbs or all four limbs or with systemic lymphatic channel involvement. Generalized warty lesions appear during adolescent, involving palms, soles and anogenital region. Histological evaluation of anal region reveals dysplasia.

Thirty years ago Ostrow et al. reported the case of a patient with similar features of WILD syndrome. A 37-year-old white man without family history of lymphedema presented with congenital lymphatic disease on all 4 extremities, and disseminated flat warts and pityriasis versicolor–like papules developed during adolescence. Further features included anergy to routine skin testing, depressed mitogen-stimulated lymphocyte transformation, severe CD4T-cell and B-cell depletion, low albumin and low total serum protein levels, and condylomatous (partially dysplastic) lesions in the anogenital region.¹

Kreuter A et al. described a 37-year-old German woman with primary lymphedema presented for evaluation of persisting generalized warts that appeared during adolescence. Lower extremity edema was first noted at 6 months of age, and later progressed to involve the groin, vulva, anal region, and distal upper extremities. Results of laboratory investigations revealed a notable lymphopenia level of 500/μL (reference range, 1000-4050/μL), a low total protein level of 5.4 g/dL (reference range, 6.4-8.3 g/dL), and low albumin levels. Immunoglobulin levels were within reference range but decreased CD4+ and CD8+ T cell count. Histopathology evaluation
of the red and brown wart-like lesions showed characteristic of cutaneous warts. Specimens of several verrucous lesions of the anogenital region including the vulva, perianal skin, and anal canal revealed intraepithelial neoplasia grades I to II.  

In comparison to the above two cases, our patient had similar features with systemic involvement of primary lymphedema.

**Conclusion**

We can finally conclude that this patient is suffering from WILD syndrome although further molecular investigations like genetic mutation studies are needed to confirm which are not available in our country.

**References**