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Research Letter

Clinical Report of Congenital Lymphatic Malformations and Partial Gigantism of the Hands Associated with a Heterogeneous Karyotype

To the Editor:

Partial gigantism of the hands is a component of Proteus syndrome (OMIM 176920) [Wiedemann et al., 1983], Klippel–Trenaunay syndrome (OMIM 149000) [Cohen, 2000], and other disorders. One cause of partial gigantism can be congenital lymphatic malformations, which are in turn characterized by cystic dilatation of the lymphatic vessels [Greenlee et al., 1993; Fonkalsrud, 1994].

We recently observed a 45-year-old woman with partial gigantism of the hands and multiple lymphatic malformations. At birth, her hands were enlarged. The right index finger was amputated because it impaired hand function when she was 5-years-old. Other congenital anomalies included subcutaneous masses in the left axillary fossa and on her back. The masses grew as the patient grew, and had unexplained intermitting disappearances and reappearances. At 45-years-old, the patient was admitted to a hospital because of colporrhagia of 3 months duration and was diagnosed with atypical endometrial hyperplasia and splenomegaly. She underwent a hysterectomy and splenectomy. There is no family history of either lymphatic malformations or gigantism of the hands.

The patient's facial features were normal. Partial gigantism of the hands was present (Fig. 1) with many overgrown phalanges of her hands in X-ray images (Fig. 2). Multiple masses were palpable in left axillary fossa and in the back and abdomen. Computed tomography and ultrasound showed multiple cystic masses in the liver, spleen, left axillary fossa (Fig. 3), right upper clavicle, mediastinum, bilateral ovaries, and subcutaneous tissue of her back. Pathologic analysis showed that the spleen was $40 \times 19 \times 12$ cm^3, consisting of large cysts with associated multiple small subcapsular cysts containing clear, yellow fluid. Histology showed the cysts of spleen were lined by endothelium, the walls of the cysts consisted of smooth muscle cells and collagen.

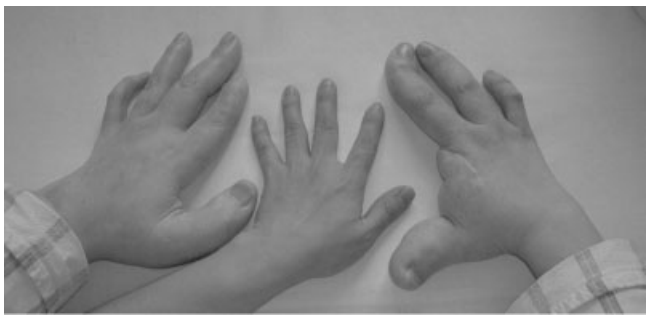

Fig. 1. The hands of the patient. Note the fingers were longer and thicker than the fingers of a normal adult hand (middle).

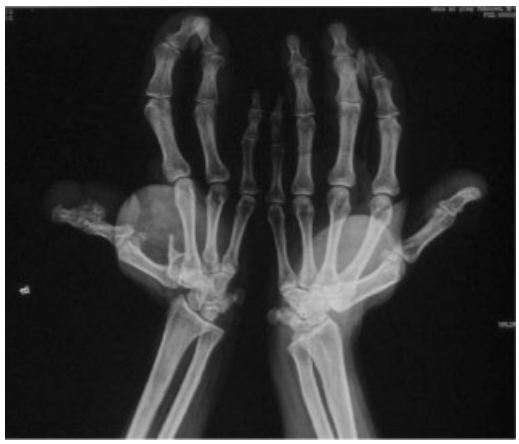

Fig. 2. X-ray of the hands showing hypertrophy of many phalanges.

Fluorescence in situ hybridization (FISH) and spectral karyotyping (SKY) was performed as described earlier [Padilla-Nash et al., 2001]. The histological features of the splenic cysts were consistent with dilated lymphatic channels.

SKY of peripheral blood leukocytes revealed a composite karyotype (Fig. 4A), mos 46,XX[12]/46,XX,ish del(17)(p12-p13)(*TP53*)[5]/47,XX,+X[2]. FISH using a *TP53*-specific gene probe for the 17p13.1 locus and a whole chromosome paint for X was performed to further investigate the del(17) and to verify an extra copy of X as seen in SKY. Eleven cells were analyzed: five cells (46%) demonstrated two normal *TP53* signals; four

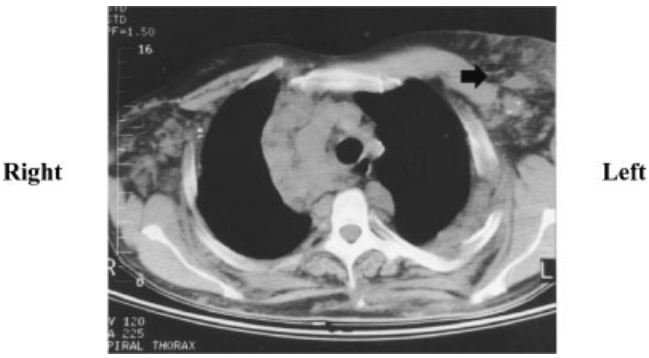

Fig. 3. Cystic masses in the left axillary fossa shown by computer tomography.

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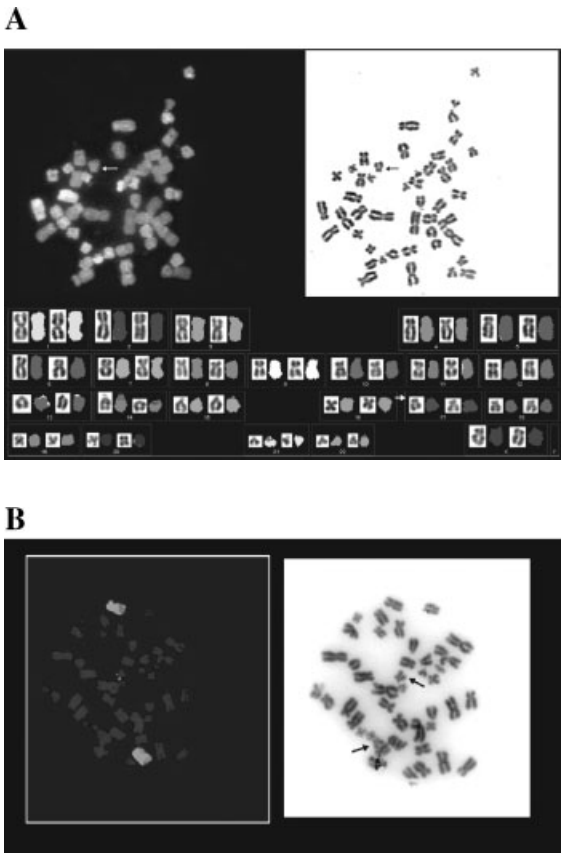

Fig. 4. **A**: Spectral karyotype of peripheral blood cells. Arrows indicate the possibly deleted chromosome 17. **B**: FISH showed only one positive signal for the 17p13.1 locus. Arrows indicate both normal and aberrant chromosome 17's in the DAPI image. The X chromosome is painted in green, with a whole chromosome paint and the *TP53* gene probe is labeled with spectrum orange (Vysis Inc., a wholly-owned subsidiary of Abbott Laboratories, 3100 Woodcreek Drive, Downers Grove, IL 60515-5400).

cells demonstrated one weak and one strong signal, indicative of a partial deletion within the region of the FISH probe; and two cells (18%) demonstrated only one signal (Fig. 4B), indicating a deletion of the *TP53* region encompassed by the FISH probe on one homologue, this is suggestive of a mosaic karyotype. No extra copies of the X chromosome were detected by FISH in these 11 cells, although we cannot exclude that 47,XXX may be present at a low frequency.

These results suggest that the genesis of combined congenital multiple lymphatic malformations and partial gigantism of the hands in this patient may be related to trisomy of the X chromosome or partial loss of the *TP53* gene locus. No similar clinical syndrome has previously been associated with deletions of 17p12-13. This patient did not meet the criteria of Proteus syndrome [Biesecker et al., 1999], Klippel–Trenaunay–Weber syndrome [Berry et al., 1998], and Van Buchem Disease (OMIM 239100) [Van Hul et al., 1998]. We conclude that the condition in this patient is distinct from these known syndromes and may be caused by this mosaic chromosome constitution.

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