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LYMPHSPIRATION

PRIMARY LYMPHEDEMA AND ACUTE LEUKEMIA – IS THERE A LINK?

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ABSTRACT

The lymphedema service in Glasgow has been treating patients with lymphedema of all causes since 1991. In the past five years 3 patients with primary lymphedema have been diagnosed with myelodysplasia (leading to acute leukemia) or acute leukemia. These are relatively unusual malignancies given the ages of the patients and all three of these patients died within an average of 12 months of diagnosis. A connection between the presence of primary lymphedema and the subsequent development of the hematological disorder is postulated. Standard marrow cytogenetics failed to identify a common abnormality but the authors feel that further study is warranted.

Keywords: primary lymphedema, acute leukemia, myelodysplasia

The lymphedema service in Glasgow has been treating patients with lymphedema of all causes since 1991. Eighty-nine (15%) patients currently attending the clinic have primary lymphedema from a total of 600 registered with the service. Primary lymphedema is the term given when the lymphatics have a direct pathological fault (1) often in the form of a congenital abnormality in the lymphatics. Swelling can present at any time from birth to later life (2) and usually occurs in one or more of the limbs but can also be present in the trunk, face or deeper organs depending on the extent and area of the malformation. Primary lymphedema is uncommon: Dale (1) has estimated a frequency of 1 in 6000 with a sex ratio of approximately one male to three females.

Since 2005, we have observed 3 primary lymphedema patients developing myelodysplasia (leading to acute leukemia) or acute leukemia *de novo*. Unfortunately despite aggressive treatment of the leukemias in regional hematological centers using contemporary clinical trial protocols all 3 of these patients have died (*Table*) .

Epidemiology of Acute Leukemia

Leukemia remains a relatively rare disorder in terms of absolute risk. Acute lymphoblastic leukemia (ALL) is the commonest form in childhood, and Acute Myeloid Leukemia (AML) the commonest in older adults.

ALL has a crude incidence rate of 1.5 cases per 100,000 patient years although by far and away the bulk of these occur in the under 10s (3). It is particularly rare in middle aged adults, as with our patient. AML has a

TABLE
Patient Details

Case/Sex	Age of onset of lymphedema	Site of swelling	Organ involvement	Type of leukemia	Bone marrow cytogenetics	Age of onset/ Age of death
1/Female	5	Both legs over 3 week period. Suprapubic area at assessment.	No	Acute Myeloid Leukemia	46XX	10 / 12
2/Male	9	Legs, scrotum, and penis	Lungs and bowel	Myelodysplasia and secondary AML	45 XY	16/17
3/Female	present at birth	Both legs and and feet	Bowel and lungs	Acute lympho-blastic leukemia	Complex ALL associated karyotype. See legend for full details.*	35/35

*Case 3 had complex cytogenetic abnormalities identified in 39/44 cells by routine karyotyping and confirmed by FISH, as follows: 45, XX, der(9)add(9)(p11)add(9)(q22), -20[22}/45,XX,der(16)t(1;16)(q21;q12.1),-20[8]/45, Xxder(17)t(1;17)(q25;p11),-20[2]/46,XX,del(9)(p21),-20,+mar[3]/46,XX,del(9)(p21),der(16)t(1;16)(q21;q12.1), -20,+mar[2]/45,XX,dic(9;20)(p11;q11),der(16)t(1;16)(q21;q12.1)[2]/46,XX[5].

rate of 4.2 cases per 100,000 patient years (4) and the bulk of these are in later years (only 5% of cases occur in people under 20 years of age).

Genetics

A study by Parry (5) in 1994 reports an association between different types of leukemias and chromosomal abnormalities involving 11q23. The transcription factor produced from this locus possessed a high degree of similarity to the forkhead transcriptors, abnormalities of which have been shown to be associated with primary lymphedema (6). Human forkhead genes however are spread throughout the genome. *FOXC2* (a forkhead transcriptor) mutations are also associated with yellow nail syndrome (7). Turner's syndrome is also associated with lymphedema and there are several references to leukemia and Turner's syndrome in the literature though an actual correlation has not been established (8).

Milroy (9) in 1892 was the first to recognize a definite family history of lymphedema. Milroy's disease has a triad of features: family history of lymphedema, lymphedema of the lower limbs, and present at birth. The condition is linked to an abnormality at 5q35.3 which localizes to the VEGFR-3 locus. Failure of lymphangiogenesis due to lack of activity of VEGFR-3 seems to be the defect in the inheritance of Milroy's disease (10). The lymphedema-distichiasis syndrome is thought to be secondary to an abnormality at chromosome 16q24.3 (11). Mutations in *FOXC2* have been shown to be responsible for the hereditary lymphedema-distichiasis syndrome (6). The presence of primary lymphedema is associated with many phenotypical variations and there are likely to be several sites of gene mutation responsible.

Standard marrow cytogenetics carried out on our 3 cases presented failed to identify any common chromosomal abnormalities (*Table*).

DISCUSSION

While 3/89 primary lymphedema patients have developed myelodysplasia or acute

leukemia, there were no other cases of leukemia in the other 511 in our practice patients with secondary lymphedema. It is therefore tempting to speculate that there may be a link between the hematological disorder and primary lymphedema (12,13). Potential mechanisms might include ineffective immune surveillance in the affected area, or a common genetic abnormality acting as a "first hit." While the latter might be less likely given the disparate types of hematological malignancy involved, a possible genetic link has been suggested in previous case reports. Standard marrow cytogenetics, although very useful in classifying and risk-stratifying acute leukemia, is a relatively crude method of detecting genetic abnormalities (i.e., it will not identify point mutations, only gross chromosomal structural or numerical abnormalities). It is, therefore, not surprising that no common link was established using this methodology.

CONCLUSION

Although our absolute numbers are small, these are unusual cases for the ages of the patients involved in terms of the types of leukemia. Standard cytogenetics of the patients with leukemia failed to identify any common chromosomal abnormalities. Further study of the potential link between primary lymphedema and leukemia, however, is warranted. One method would be a national registry of all such patients to allow long-term follow-up and identification of any associations between primary lymphedema and leukemias.

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