Molecular Heterogeneity of ALK-negative Anaplastic Large Cell Lymphoma

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OBJECTIVES

Anaplastic large cell lymphomas (ALCLs) are CD30-positive T-cell lymphomas that may be ALK-positive or ALK-negative by current WHO criteria. While ALK-positive ALCLs consistently have *ALK* rearrangements, the molecular pathogenesis of ALK-negative ALCLs is poorly understood. We previously identified recurrent rearrangements of the *DUSP22* and *TP63* loci in ALK-negative ALCLs and sought to study the frequency, morphology, phenotype, and clinical outcomes associated with these rearrangements.

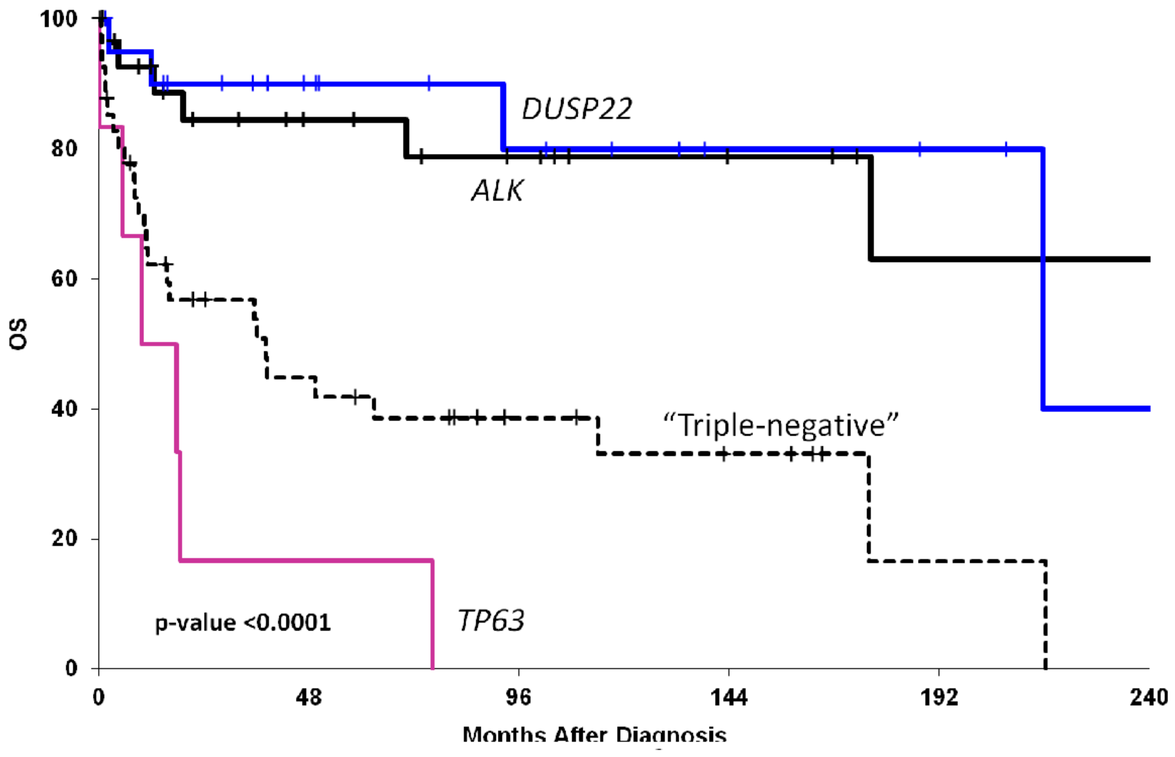
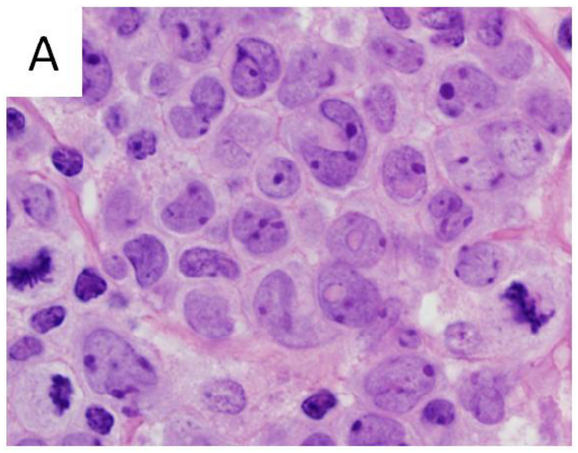
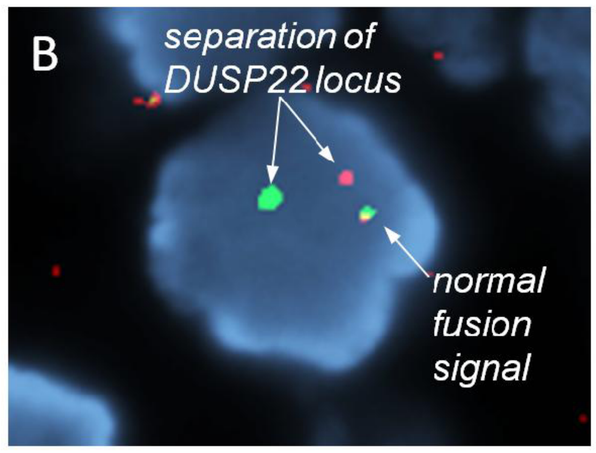


Fig. 1. Overall survival of ALCL stratified by genetics.





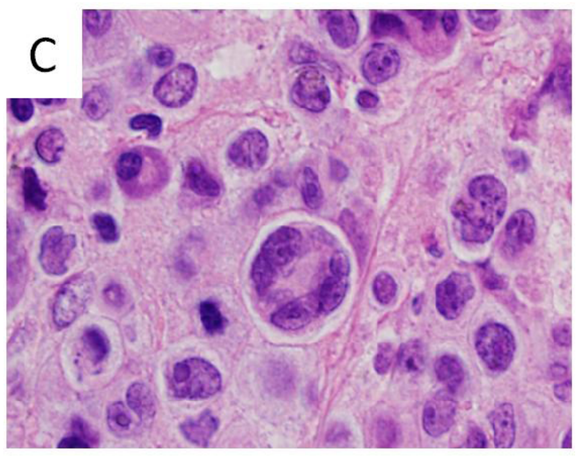


Fig. 2. Morphology of ALK-negative ALCL. A. *DUSP22*-rearranged ALCL with hallmark and doughnut cells. B. FISH with breakapart probe showing separation of *DUSP22* locus. C. Triple-negative ALCL showing large cell with wreath-like nucleus.

METHODS

Paraffin sections of systemic ALCLs were examined for *DUSP22* and *TP63* rearrangements by FISH. The primary clinical endpoint was overall survival (OS). Morphologic features were scored in a blinded fashion. Phenotype was assessed by immunohistochemistry and RNA-ISH for the chemokine receptor gene *CCR8*. T-cell receptor (TCR) gene rearrangements were assessed by NGS of mate-pair DNA libraries and PCR.

RESULTS

Among 73 ALK-negative ALCLs, 30% had *DUSP22* rearrangements and 8% had *TP63* rearrangements. These were mutually exclusive, and neither was present in 32 ALK-positive ALCLs. ALCLs with *DUSP22* rearrangements had a 5-year OS rate of 90%, similar to ALK-positive ALCLs (85%) and superior to ALCLs with *TP63* rearrangements (17%) or "triple-negative" ALCLs lacking all 3 rearrangements (42%; p=0.0001; Fig. 1). ALCLs with *DUSP22* rearrangements showed sheet-like growth of hallmark cells with increased "doughnut" cells (p=0.039) and fewer pleomorphic cells (p=0.042; Fig. 2). These features correlated with the presence of *DUSP22* rearrangements in an independent validation cohort (p<0.0001). ALCLs with *DUSP22* rearrangements generally lacked expression of cytotoxic markers (e.g. TIA-1, p<0.0001) and showed increased expression of *CCR8* (p=0.0008; Fig. 3). ALCLs with *DUSP22* rearrangements all had clonal TCR gene rearrangements (100%); the frequency of clonal rearrangements was lowest in triple-negative ALCLs (53%; p=0.029).

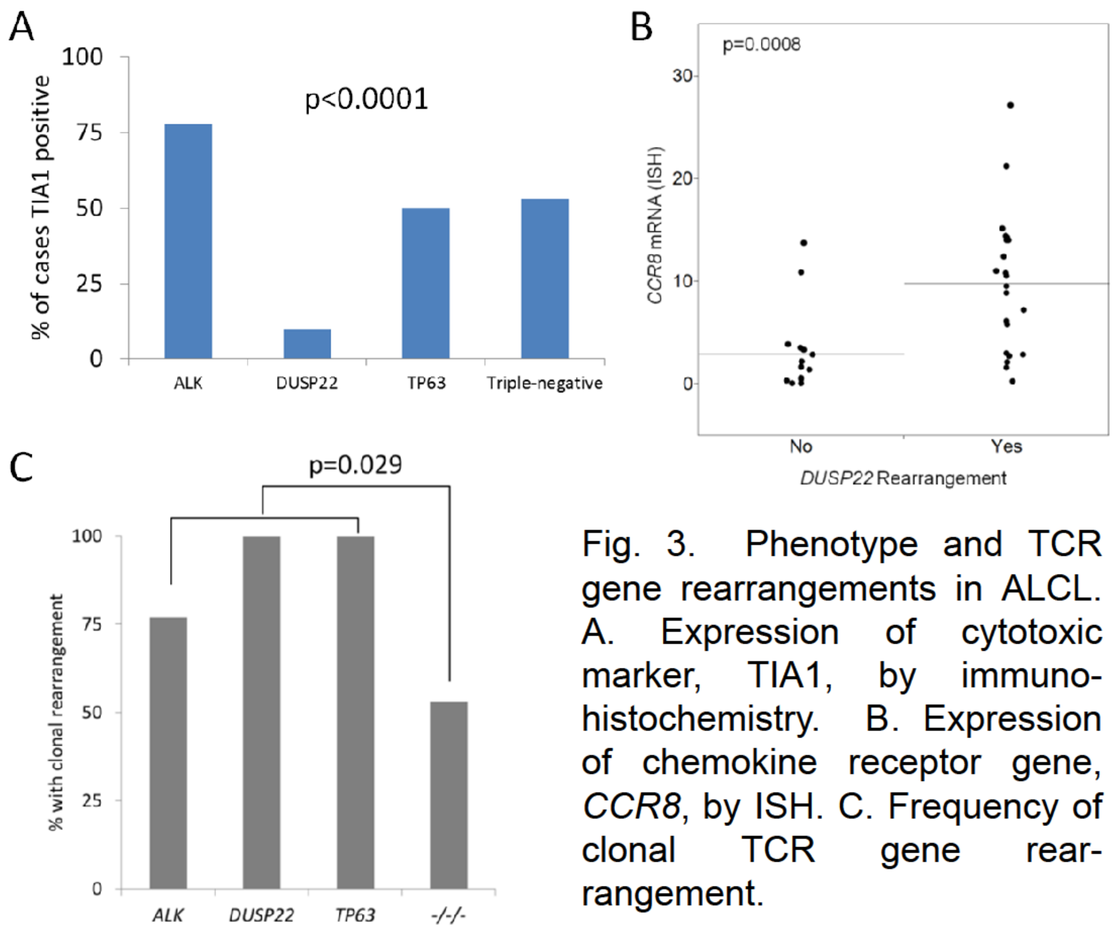


Fig. 3. Phenotype and TCR gene rearrangements in ALCL. A. Expression of cytotoxic marker, TIA1, by immuno-histochemistry. B. Expression of chemokine receptor gene, *CCR8*, by ISH. C. Frequency of clonal TCR gene rearrangement.

CONCLUSIONS

ALK-negative ALCLs demonstrate pathologic, molecular, and clinical heterogeneity. *DUSP22* rearrangements occur in 30% of cases and are associated with classic ALCL morphology, lack of cytotoxic marker expression, and excellent outcomes. The role of *CCR8* in T-cell trafficking to skin and other sites and the observation that *DUSP22* rearrangements also occur in 28% of primary cutaneous ALCLs suggest that systemic and primary cutaneous cases with this rearrangement share some biologic features. ALCLs with *TP63* rearrangements are less common and remain poorly understood. Their very poor prognosis indicates a need for further study of their clinicopathologic features, biology, and potential for targeted therapies. FISH for both rearrangements can be performed easily in the clinical setting.

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References

1. Feldman AL et al. Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. Blood. 2011; 117:915-9.
2. Vasmatzis G et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. Blood 2012;120:2280-9.
3. Parrilla Castellar ER et al. ALK-negative anaplastic large cell lymphoma is genetically heterogeneous disease with widely disparate clinical outcomes. Blood 2014;124:1473-80.
4. Xing X et al. Expression of the chemokine receptor gene, CCR8, is associated with *DUSP22* rearrangements in anaplastic large cell lymphoma. Appl Immunohistochem Mol Morphol 2014 Nov 11 [Epub ahead of print].
5. King RL et al. Morphology of ALK-Negative Anaplastic Large Cell Lymphomas with *DUSP22* Rearrangements. Am J Surg Pathol (in press).
6. Kip NS et al. T-cell Receptor Gene Rearrangements with Anaplastic Large Cell Lymphoma: Associations with Pathology and Genetics. Lab Invest 2015; 95:355A.

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T-cell lymphoma
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