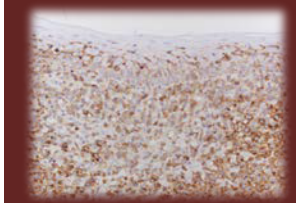
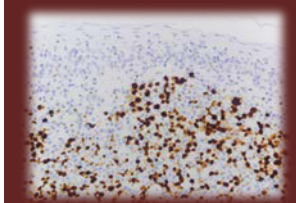
Case Presentation 15 - *Post Transplantation IRF Trans location + ALCL*

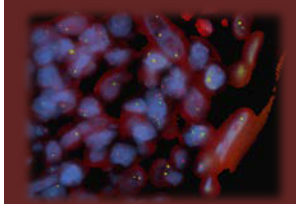
Case Author: Cynthia M. Magro, MD

Contributing Authors: Martha Torres, MD, Esther Chang, MD, Luke Olsen, MD, & Shivakumar Subramaniyam, MD

Weill Cornell Medicine Dermatopathology







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Case Report

An 81-year-old male received a heart transplant in 1998 for idiopathic cardiomyopathy. The procedure was uneventful without any immediate complications. He was treated with azathioprine (50 mg) and cyclosporine (25 mg) for long-term immunosuppression with a brief period of concurrent prednisone in the distant past. Other than mild cyclosporine-related renal insufficiency, his clinical course was unremarkable.

In November 2014, he presented with a history of an expanding neck lesion. Physical examination revealed a 2.2 cm non-painful nodule on the right neck. The patient was otherwise asymptomatic. An excisional biopsy of the nodule was performed. A PET scan was performed in January 2015 to rule out an occult malignancy but was negative for metastatic disease. Azathioprine was removed from his medication regimen as he was considered to be at low-risk for rejection. Clinical follow-up showed no evidence of disease progression as of the time of manuscript submission in March 2015.

Histopathological Features

The excision of the right neck nodule revealed an effacing nodular atypical mononuclear cell infiltrate spanning the papillary and reticular dermis. There was no grenz zone separating the infiltrate from the overlying epidermis (Figure A, B). The epidermis was diffusely infiltrated in a passive epidermotropic fashion by small to intermediate sized atypical lymphocytes exhibiting a cerebriform morphology (Figure C). In contrast, the populace in the dermis was comprised of large (20-30 um) relatively monomorphic transformed-appearing cells with round to oval nuclei and conspicuous nucleolation; cytoplasms were moderately abundant (Figure D). Mitoses were abundant within the dermal population. There was a relative paucity of other inflammatory cell elements.

Immunohistochemical Findings

Several immunohistochemical studies were performed. Staining for CD3 (Figure E) and CD30 (Figure F) was positive in all neoplastic cells within the epidermis and dermis. The tumor cells were positive for MUM-1 within he dermal populace while the neoplastic cells in the epidermis did not stain positively for MUM-1. There was focal immunoreactivity of the tumor cells for CD4, CD56 and CD57. Staining for CD5, CD7, CD8, CD20, and PD1 was negative. Granzyme and T-cell intracytoplasmic antigen (TIA-1) studies were negative denoting a non-cytotoxic phenotype. Evidence of EBV infection was also not observed as both EBER and latent membrane protein stains were negative.

Cytogenetics

FISH was performed on paraffin embedded tissue per standard protocol using the Repeat-FreeTM PoseidonTM IRF4/DUSP22 (6p25) Break Probe (KI-10613) trademarked by Kreatech Diagnostics. The epidermis and dermis were subsequently screened for rearrangements of the 6p25.3 locus.

A break-apart interphase FISH assay revealed rearrangement of the DUSP22/IFR4 genes in 75% of the cells. Of note, this translocation was seen in both the epidermal and dermal lymphocyte populations despite the varied immunoreactivity for MUM-1 (Figures G.H).

Discussion

The majority of systemic post-transplant lymphoproliferative disorders are EBV-associated B cell neoplasms that develop within the first few years following transplantation. Similar to other cases of cutaneous T-cell PTLD, this patient's lymphoma was negative for any evidence of EBV infection and occurred many years subsequent to the transplantation. It has been postulated that T-cell PTLDs are fueled by an alternative viral infection, such as HHV-8 or HTLV-1; however, examples of PTLDs related to these agents have only been described in rare forms of post-transplant T-cell lymphoma in select case series. Perhaps a more likely explanation for post-transplant T-cell lymphoproliferative disorders relates in part to the direct immune modulating effects of immunosuppressive medications. For example, it has been hypothesized that a decrease in regulatory T-cell production induced by these agents could allow for uninhibited proliferation of T-cell clones, such as those responding to EBV-infected B cells, leading to unopposed neoplastic progression. The response of at least some of these neoplasms to a reduction or cessation of these drugs emphasizes the role of drug therapy in the propagation of PTLD Seventeen other cases of primary cutaneous anaplastic large cell lymphoma in the post transplant setting have been reported represented by 11 kidney transplant patients(10 months to 16 years following transplantation) , two liver transplant patients (5 years and 9 years following transplantation) and four heart transplant patients(7,15,10 and 11 years after transplantation). All but three patients experienced complete regression with any one or more of radiation, chemotherapy and or surgical removal. In one case a reduction in immunosuppressive therapy was effective in achieving complete remission. Three patients died.

Feldman and co-workers were the first to identify the presence of IRF4 translocations in the setting of cutaneous anaplastic large cell lymphoma in 2009 (Feldman et al 2009). The authors identified recurrent translocations involving the multiple myeloma oncogene-1/interferon regulatory factor-4 (IRF4) locus and identified 12 cases with IRF4 translocations amidst 178 cases studied of peripheral T cell lymphoma . The spectrum of T cell disorders studied included cutaneous anaplastic large cell lymphoma, systemic anaplastic large cell lymphoma, lymphomatoid papulosis, mycosis fungoides/Sezary syndrome, peripheral T-cell lymphoma, CD4-positive small/medium-sized pleomorphic T-cell lymphoma, extranodal NK/T-cell lymphoma nasal type, gamma-delta T cell lymphoma, and other rare T-cell lymphomas. The translocation was discovered in 11 cases of primary cutaneous anaplastic large cell lymphoma. All 133 non-cALCL cases were negative for the translocation except for one case of lymphomatoid papulosis (Feldman et al 2009). Another group of authors examining a spectrum of primary cutaneous T cell lymphoproliferative disorders established that the detection of the IRF4 translocation was associated with a specificity and positive predictive value of 99% and 90% respectively for a diagnosis of primary cutaneous anaplastic large cell lymphoma (Wada et al 2011) . Another study on primary cutaneous T cell lymphoproliferative lesions associated with CD30 positivity found that such translocations were highly specific for a diagnosis of primary cutaneous anaplastic large cell lymphoma (Kiran et al 2013) However in the study conducted by Pham-Ledard and co-workers discovered a translocation at the IRF4 locus in 6 out of 23 C-ALCL (26%) and 2 out of 11 T-MF (18.2%) cases. Extra copies of the IRF4 locus were found in 4 out of 13 Sezary syndrome, 1 out of 11 tumor stage mycosis fungoides cases and 1 out of 23 cutaneous ALCL cases, corresponding to either aneuploidy, chromosome 6 trisomy, or 6p partial gain(Pham-Ledard et al 2010).

The histologic pattern seen for CD30+ T cell lymphoproliferative lesions exhibiting the 6p25.3 translocation is highly distinctive comprising a distinct pattern of small cell epidermotropic T cell infiltration recapitulating a pagetoid reticulosis-like morphology in concert with an effacing nodular growth of transformed cells in the dermis. The morphologic overlap between cases of primary cutaneous anaplastic large cell lymphoma associated with this distinctive translocation versus lymphomatoid papulosis lesions manifesting the 6p25.3 translocation is striking and suggests a clinical and pathologic continuum (Onaindia et al; Karai et al 2013) .

In summary we have reported a case of post transplant anaplastic large cell lymphoma associated with a distinctive histology and cytogenetic profile characteristic for IRF translocation positive ALCL. To our knowledge, this is the first reported case of post transplantation IRF trans location + ALCL and serves to underscore the potential importance of long standing iatrogenic immune dysregulation in its evolution. Whether or not other reported cases of post transplant ALCL harbored this translocation is unclear but evaluation of future cases of post transplant ALCL will provide a further clarification regarding the frequency of the IRF4 translocation in this unique clinical setting.

Figure Legend

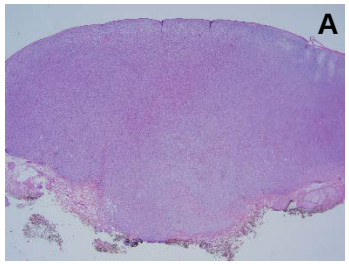


Figure A: This low power view shows an extensive nodular lymphocytic infiltrate that is permeative of the epidermis. It is a sharply circumscribed infiltrate that involves the dermis. Note the pushing nodular border towards the base. The typical eccrinotropic and perineural accentuation seen in LYP is not seen. .

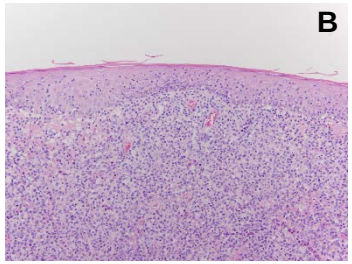


Figure B: There is a strikingly epidermotropic lymphocytic infiltrate whereby there is a disparity between the small cell dominant infiltrates present in the epidermis juxtaposed to the larger cell infiltrate in the subjacent dermis.

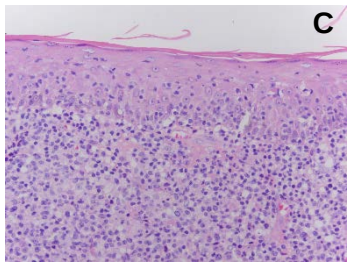


Figure C: Higher power magnification shows an epidermotropic pattern of lymphocytic infiltration that is quite analogous to what one would encounter in mycosis fungoides although clearly the infiltrate within the subjacent dermis is quite disparate to that encountered in conventional mycosis fungoides based on the large dominant large cell quality of the infiltrate within the dermis.

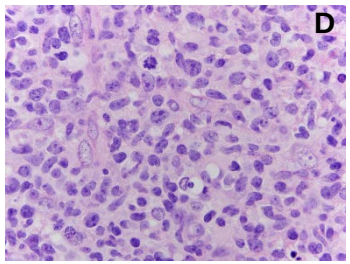


Figure D: Examination under oil reveals the malignant large cell hematopoietic populace that dominates the dermal infiltrate. There are a few smaller lymphocytes although clearly the main cell population is in the 30 micron size range with a vesicular chromatin and prominent eosinophilic nucleoli.

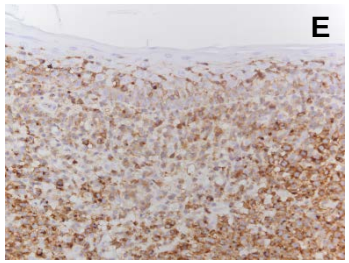


Figure E: A CD30 preparation shows very extensive immunoreactivity of the neoplastic cells both within the epidermis and dermis..

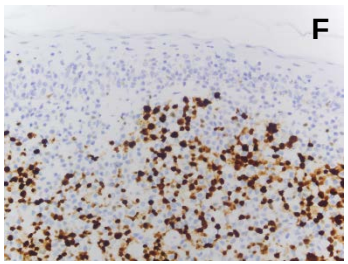
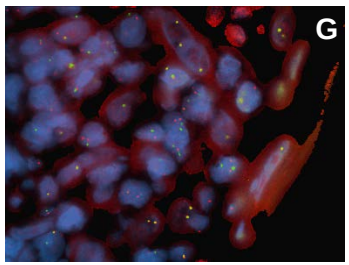
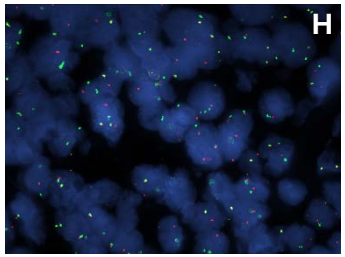


Figure F: There is overexpression of the neoplastic cells within the dermis for MUM1. Interestingly the epidermotropic small cell populace is MUM1 negative emphasizing that this cytogenetic abnormality has no influence on IRF4 protein expression





Figures G.H: The probe used was DUSP22/IRF4 dual color break apart probe (Kreatech Diagnostics, IL). Two hundred cells were scored. 75% were positive for rearrangement of DUSP22/IFR4 both in epidermis and dermis area. The cytogenetic studies were performed by Dr. Shivakumar Subramaniyam Ph.D, FACMG, Weill Cornell Medical College, NewYork Presbyterian Hospital (Figures E,F)

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Under the direction of Dr. Cynthia M. Magro, the Weill Cornell Comprehensive Dermatopathology Service is a leading edge consultation service and CAP-accredited laboratory for dermatologists, plastic and general surgeons and other dermatopathologists. Dr. Magro is an internationally renowned dermatopathologist, educator and author. She is a Professor of Pathology and Laboratory Medicine at the Weill Cornell Medical College in Manhattan, and is board certified in anatomic pathology, dermatopathology and cytopathology. Dr. Magro is an expert in the diagnosis of complex inflammatory skin diseases. Her areas of expertise include cutaneous manifestations of auto-immune disease, systemic viral disease and vasculitis, atypical drug reactions, benign, atypical and overtly malignant lymphocytic infiltrates of the skin, and diagnostically difficult melanocytic proliferations.The award-winning author of *The Melanocytic Proliferation: A Comprehensive Textbook of Pigmented Lesions*, Dr. Magro has recently completed her second book, *The Cutaneous Lymphoid Proliferation, a comprehensive textbook on benign and malignant lymphocytic infiltrates*. She has co-authored over 280 peer reviewed papers and several textbook chapters. Dr. Magro frequently presents courses on inflammatory skin pathology and difficult melanocytic proliferations to the American Academy of Dermatology, the United States and Canadian Academy of Pathology, and the American Society of Clinical Pathology. Dr Magro has consistently been recognized in Who's Who in America®, Castle Connolly's renowned America's Top Doctors – New York Metro Area® edition and in the Super Doctors® list published in The New York Times Magazine.

For more information, consultation, or patient referral please contact:

Cynthia M. Magro, MD
Director
Weill Cornell Comprehensive Dermatopathology Service
Tel. 212-746-6434
Toll-free 1-800-551-0670
ext. 66434
Fax. 212-746-8570
www.weillcornelldermpath.com