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Case reviews for Elidel and lymphoma  
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I. Case 1:

A 61 year old woman who apparently developed histiocytic lymphoma after only a few weeks of exposure to Elidel treatment.

1. Additional info: Evaluating the tissue would be useful (true histiocytic lymphoma is quite rare). Obtaining serology to document HIV and HCV status would have been useful. What was the patient's history for tobacco use and what was the duration of the patient's exposure to hair dye?

2. Causal association: in my opinion, it is extremely unlikely that this patient developed lymphoma on the basis of Elidel therapy.

3. Explanation: The interval between duration and development of lymphoma is so short it is more likely that the patient already had contracted lymphoma at the time the Elidel was initiated. In fact, there is an association between eczema and the subsequent development of lymphoma (see citation below).

4. Citations:

Zhang Y, Holford TR, Leaderer B, Zahm SH, Boyle P, Morton LM, Zhang B, Zou K, Flynn S, Tallini G, Owens PH, Zheng T. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. *Cancer Causes Control* 2004; 15: 419-428.

[This study showed that eczema or atopic dermatitis appears to be a risk factor for the development of lymphoma].

Miligi L, Seniori Costantini A, Crosignani P, Fontana A, Masala G, Nanni O, Ramazzotti V, Rodella S, Stagnaro E, Tumino R, Vigano C, Vindigni C, Vineis P. Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. *Am J Ind Med* 1999; 36: 60-69.

[This study addressed the increased association of tobacco use as well as hair dyes and increased risk of lymphoma].

Morton LM, Engels EA, Holford TR, Leaderer B, Zhang Y, Zahm SH, Boyle P, Zhang B, Flynn S, Tallini G, Owens PH, Zheng T. Hepatitis C virus and risk of non-Hodgkin lymphoma: a population-based case-control study among Connecticut women. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 425-430.

Zhang Y, Holford TR, Leaderer B, Boyle P, Zahm SH, Flynn S, Tallini G, Owens PH, Zheng T. Hair-coloring product use and risk of non-Hodgkin's lymphoma: a population-based case-control study in Connecticut. *Am J Epidemiol* 2004; 159: 148-154.

Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor KP, Blair A. A case-control study of tobacco use and other non-occupational risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma (United States). *Cancer Causes Control* 2002; 13: 159-168.

Besson H, Renaudier P, Merrill RM, Coiffier B, Sebban C, Fabry J, Trepo C, Sascó AJ. Smoking and non-Hodgkin's lymphoma: a case-control study in the Rhône-Alpes region of France. *Cancer Causes Control* 2003; 14: 381-389.

## II. Case 2:

A two year old infant male developed a lymphoblastic lymphoma within 6 months after exposure to Elidel.

1. Additional info: The biopsy should be reviewed for histology, immunophenotyping and EBV status. Obtaining serology to HIV and HCV would have been useful. The disease extent and sites, including presence/absence of marrow involvement, are important factors. Further, did this patient have any underlying medical conditions or family history suggesting a predilection for the development of lymphoma.

2. Causal association: in my opinion, it is extremely unlikely that this patient developed lymphoma on the basis of Elidel therapy. This lymphoma subtype (if confirmed histologically), although uncommon, typically affects young individuals and presents in the mediastinum (not an atypical location) such as in this patient.

3. Explanation: The interval between duration of Elidel therapy and development of lymphoma is relatively short; it appears quite unlikely that this agent was causal. Further, eczema or atopic dermatitis appears to be a risk factor for the development of lymphoma

### 4. Citations:

Zhang Y, Holford TR, Leaderer B, Zahm SH, Boyle P, Morton LM, Zhang B, Zou K, Flynn S, Tallini G, Owens PH, Zheng T. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. *Cancer Causes Control* 2004; 15: 419-428.

[This study showed that eczema or atopic dermatitis appears to be a risk factor for the development of lymphoma].

Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. *Clin Lymphoma* 2003; 4: 161-168.

### III. Case 3:

A patient with an apparent history of vitiligo reportedly developed lymphoma (unknown patient age, lymphoma type) after exposure to Elidel (unknown duration of exposure).

1. Additional info: One needs to obtain data to support the diagnosis of lymphoma and the extent of Elidel exposure.

2. Causal association: There are insufficient data to document the occurrence of lymphoma.

3. Explanation: There are no objective data to support a relationship between lymphoma diagnosis and Elidel use. Vitiligo is an autoimmune disorder, and the latter has been noted to be a risk factor for the development of lymphoma.

#### 4. Citations:

Ramos-Casals M, Trejo O, Garcia-Carrasco M, Cervera R, De La Red G, Gil V, Lopez-Guillermo A, Ingelmo M, Font J. Triple association between hepatitis C virus infection, systemic autoimmune diseases, and B cell lymphoma. *J Rheumatol* 2004; 31: 495-499.

Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. *Oncogene* 2004; 23: 6524-6534.

Hardell L, Lindstrom G, van Bavel B, Fredrikson M, Liljegren G. Some aspects of the etiology of non-Hodgkin's lymphoma. *Environ Health Perspect* 1998; 106 Suppl 2: 679-681.

#### IV. Case 4:

A 53 year old man with a long history of generalized atopic dermatitis treated with topical immunosuppressive therapy developed a subcutaneous panniculitis-like T cell lymphoma within 6 months after exposure to Elidel.

1. Additional info: What was this man's occupation (any industrial or agriculture exposure?). Also, obtaining serology to document HIV and HCV status would be useful. What was the patient's history for tobacco use?

2. Causal association: The interval between duration and development of lymphoma is relatively short; it is more likely that the patient already had contracted lymphoma at the time the Elidel was initiated.

3. Explanation: This rare tumor appears to be a sub-set of peripheral T cell non-Hodgkin's lymphoma which generally affects the dermis and subcutaneous adipose tissue and only later affects lymph nodes. In contrast to B cell lymphomas, risk factors for the development of T cell lymphomas are less well defined. On the other hand, this patient has a long history of exposure to immunosuppressive therapy, a potential inciting factor. Further, atopic dermatitis appears to be a risk factor for the development of lymphoma.

#### 4. Citations:

Purdue MP, Bassani DG, Klar NS, Sloan M, Kreiger N; The Canadian Cancer Registries Epidemiology Research Group. Dietary factors and risk of non-Hodgkin lymphoma by histologic subtype: a case-control analysis. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 1665-1676.

[This study showed a higher rate of the development of lymphoma in patients with a high intake of processed meat, cheese or eggs or high consumption of fat.]

Hardell L, Lindstrom G, van Bavel B, Fredrikson M, Liljegren G. Some aspects of the etiology of non-Hodgkin's lymphoma. *Environ Health Perspect* 1998; 106 Suppl 2: 679-681.

[This study showed that use of chronic immunosuppressive agents can leave to the development of lymphoma.]

Stagnaro E, Tumino R, Parodi S, Crosignani P, Fontana A, Masala G, Miligi L, Nanni O, Ramazzotti V, Rodella S, Senoiri Constantini A, Vigano C, Vindigni C, Vineis P. Non-Hodgkin's lymphoma and type of tobacco smoke. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 431-437.

Chiu BC, Weisenburger DD. An update of the epidemiology of non-Hodgkin's lymphoma. *Clin Lymphoma* 2003; 4: 161-168.

Zhang Y, Holford TR, Leaderer B, Zahm SH, Boyle P, Morton LM, Zhang B, Zou K, Flynn S, Tallini G, Owens PH, Zheng T. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. *Cancer Causes Control* 2004; 15: 419-428.

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