Diffuse Alopecia Areata Associated with a Solid-Organ Malignancy: Case Report and Literature Review

A. Trink[1], Y. Ramot[2] and F. Rinaldi[1,*]

[1]*International Hair Research Foundation (IHRF), Milan, Italy*

[2]*Department of Dermatology, Hadassah – Hebrew University Medical Center, Jerusalem, Israel*

Abstract: Alopecia areata (AA) is an autoimmune disease, manifesting as non-scarring hair loss. Here we report a 57-year-old woman, who presented with sudden diffuse non-scarring hair loss on the scalp. Histology confirmed the diagnosis of AA. Imaging studies revealed the presence of an irregular mass in the left kidney, and histology demonstrated spindle cell-type renal cell carcinoma. There was spontaneous regrowth of hair after surgical and chemotherapy treatments. Reports of AA as first manifestation of malignancy are uncommon, and to our knowledge, this is the first report of AA as a paraneoplastic manifestation of renal cell carcinoma. This report also suggests that screening for malignancy should be considered in older patients, who present with sudden and diffuse AA.

Keywords: Alopecia areata, kidney cancer, autoimmune disease, paraneoplastic alopecia, hair loss disease.

INTRODUCTION

Alopecia areata (AA) is a common disease, with a calculated lifetime risk of 1.7% [1]. The disease manifests as loss of hair on virtually any hair-bearing area, but the scalp is the most common location [2]. AA usually manifests as a single patch of hair loss, but sometimes can involve the whole scalp (alopecia totalis) or the whole body (alopecia universalis) [2]. Variants of this condition include ophiasis, sisapho, and the rare variant of diffuse alopecia, which can sometimes present as the "overnight greying" phenomenon (or the Marie Antoinette syndrome) [3].

Although the exact pathogenesis of AA is unknown, it is considered to be a T-cell mediated autoimmune disease, with a strong genetic component [4]. It has been previously associated with other autoimmune diseases, and endocrine abnormalities, infectious agents, vaccinations and stress have been suggested as potential triggers [2]. Several reports have also demonstrated that AA can be associated with malignancy as a paraneoplastic syndrome [5]. Nevertheless, the link between AA and malignancy is still unclear, and is commonly regarded as coincidental. In this report, we present a patient with spindle cell-type renal cell carcinoma, who presented with diffuse AA as her first symptom. We believe that a sudden form of AA (which develops over days) in an adult over 50 years old with no previous history of AA or autoimmune disease must be evaluated for a suspected paraneoplastic AA. We present the first report, in our knowledge, of a paraneoplatic AA associated with kidney cancer.

CASE REPORT

A 57-year-old woman presented with a three-month-history of sudden and progressively worsening hair loss. Body hair was not involved in this patient. She was otherwise healthy and she did not take any medications. There was no family history of hair loss, but there was familial history of liver neoplasm (mother).

Blood tests, including complete blood cell count, routine thyroid function tests (TSH, T3, T4) and immunological tests (ANA, ENA, SMA) were all normal. Erythrocyte sedimentation rate was increased in two different evaluations (60 mm/h and 140 mm/h) suggestive of the presence of an inflammatory process.

She was previously diagnosed as having a non-specific telogen effluvium, and prescribed nutritional supplements with no therapeutical effect.

Physical examination revealed prominent diffuse non-scarring loss of hair over the entire crown with extension onto the parietal scalp (Figure **1**). Hair-pull test was positive. Histological examination of a scalp biopsy showed perifollicular lymphocytic infiltrates around anagen hair follicles, consisting of both CD4+ and intrafollicular infiltrates of CD8+ cells, without histological signs of cutaneous metastases (Figures **2**, **3**). These features, combined with the clinical signs on the scalp, were consistent with a diagnosis of diffuse AA [2].

*Address correspondence to this author at the International Hair Research Foundation (IHRF), Milan, Italy; Tel: +39 02 76006089; Fax: +39 02 89059053; E-mail: fabio.rinaldi@studiorinaldi.com

ISSN: 1927-7210 / E-ISSN: 1927-7229/14

Figure 1: Non-scarring loss of hair on the scalp.

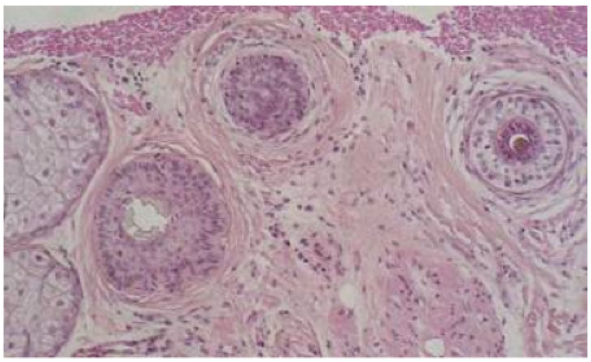

Figure 2: Horizontal sections of scalp biopsy showing perifollicular inflammatory infiltrates.

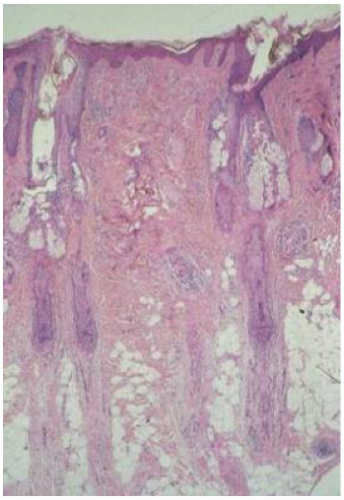

Figure 3: Vertical sections of a scalp biopsy.

On the basis of the late-onset of disease, the severity of clinical presentation and increased erythrocyte sedimentation rate, we recommended performing fecal occult blood test, chest radiography, abdominal ultrasound, and mammography. The abdominal ultrasound showed an irregular mass in the left kidney, and PET confirmed and visualized the real dimension of cancer (Figure **4**). Needle biopsy revealed a poorly differentiated renal cell carcinoma with spindle cells and bone was indicative of lymph node metastases at the basin. Patient underwent a surgical treatment and chemotherapy. After two months from the treatments the patient had a spontaneous hair re-growth (Figure **5**).

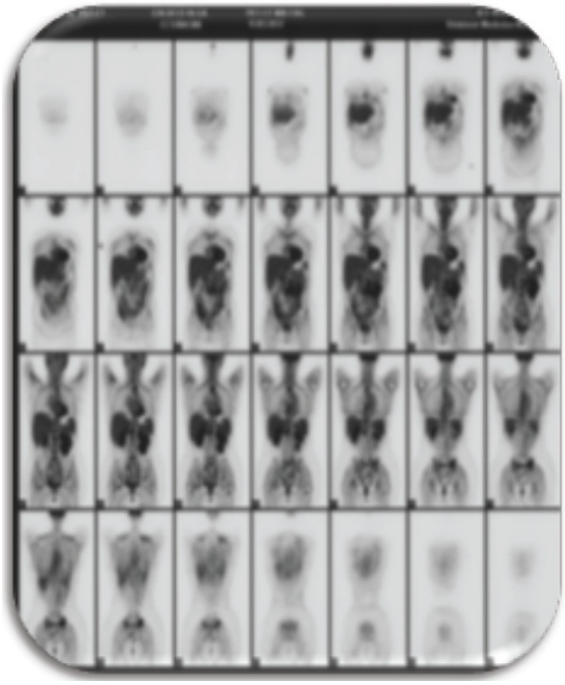

Figure 4:

Figure 5: Spontaneous regrowth of hair after surgical and chemotherapy treatment.

DISCUSSION

There are several reports linking AA with malignancy, and it was previously associated with either a solid tumor, such as thymoma [6,7], or

hematologic malignancies, such as Hodgkin's disease and acute lymphoblastic leukemia [8,9]. In a recent retrospective study of 73 late-onset AA patients from Taiwan, 8.2% had a history of malignancy, including breast cancer, cervical cancer, thyroid cancer, thymoma, laryngeal squamous cell carcinoma and transitional cell carcinoma [10]. Additional 16 AA cases were reported in which neoplasms preceded or followed the onset of AA [11,12]. The AA cases from all reports are summarized in Table **1**. To our knowledge, this is the first time that AA is associated with renal cell carcinoma.

Table 1: Cases of AA Diagnosed in Patients with Cancer

Neoplasm	Cases of AA
Thymoma	20
Hodgkin's lymphoma	2
Breast cancer	1
Lymphoblastic leukemia	1
Primary cutaneous follicle centre lymphoma	1
Cutaneous melanoma in regression	1
Cutaneous squamous cell carcinoma	1
Ovarian+uterine cancer	1
Cervical cancer	1
Laryngeal squamous cell carcinoma	1
Transitional cell carcinoma	1
Thyroid cancer	1
Gastrointestinal tumor of the esophagus	1
Gastric adenocarcinoma	1

In these patients and in our patient AA had a classic aspect of AA, and it could not be considered as a metastatic lesion, as histological examination confirmed AA in our patient. The pathogenesis of AA remains incompletely understood but it is generally regarded to be mediated by an autoimmune process [1]. It was hypothesized that pro-inflammatory cytokines in predisposed individuals cause up-regulation of ectopic MHC class Ia expression in the hair follicle, thus leading to collapse of the hair follicle's immune privilege [1]. This process is mediated by preexisting CD8+ T cells, with the help of other immune system cells. It is plausible that changes in the cellular immune system which are commonly seen in malignancies, and especially hematological ones, can presumably lead to immune collapse and the initiation of AA [13]. Neoplasm influences, which might also lead to failure to maintain epigenetic homeostasis, can cause additional immunological modifications by changing gene expression in specific cells, and afterwards to loss of tolerance [14].

It should be noted that since AA is a very common condition, and considering the fact that in some of the reported associations there was a substantial temporal gap between AA and malignancy [10], the significance of this association is still unclear, and prospective studies should be performed in order to confirm such a linkage. Nevertheless, our case, which presented with late-onset of the uncommon type of diffuse AA, combined with the severity of the disease and the rapid progression, might suggest that such a relationship is not coincidental. The spontaneous hair re-growth in this patient after cancer treatment can be considered as a meaningful connection between cancer and AA in this patient. In our opinion, unexpected and late-onset AA could be considered as a potential cutaneous symptom of cancer. Such cases might benefit from a complete blood and imaging testing to rule out malignancy.

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Received on 13-06-2014 Accepted on 12-09-2014 Published on 29-10-2014

http://dx.doi.org/10.6000/1927-7229.2014.03.04.3