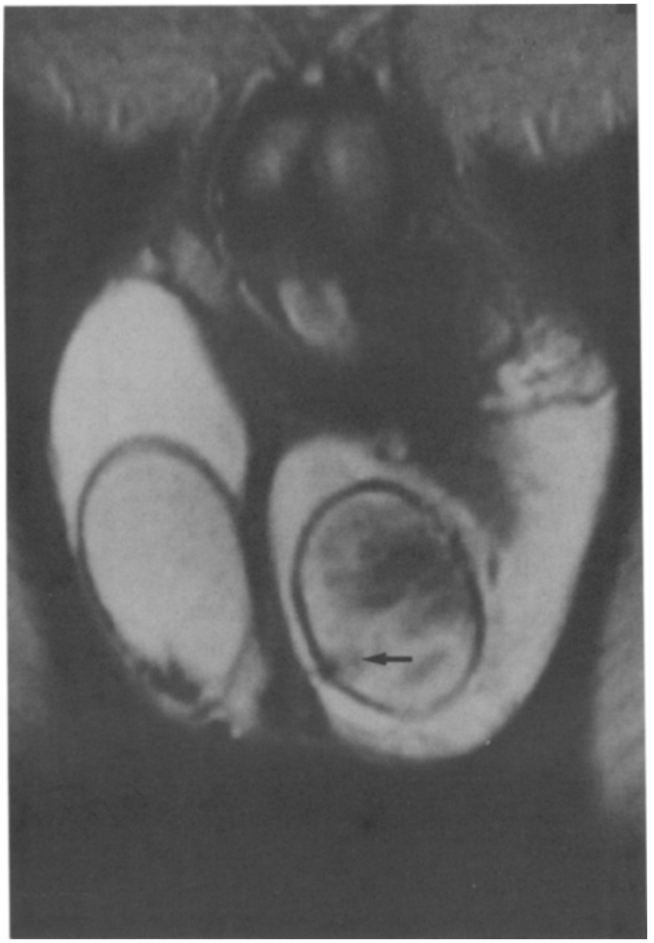

Figure 1. Magnetic resonance tomography of the left testicle 3 months after radical retroperitoneal lymph node dissection showing the tumour and the scar of the biopsy (arrow) opposite the tumour.

In this patient, the testicular origin of a supposed extragonadal germ cell tumour was diagnosed several weeks after the initial presentation. The testicular tumour was even missed by single testicular biopsy at the time of RPLND. Testicular seminoma was present all along, most probably as TIN.

There is a gradual transition from TIN to a malignant invasive tumour, and both entities are not detectable clinically or by ultrasound. During chemotherapy, these tumour cells may persist in the testicles [2]. TIN can only be diagnosed by open biopsy [3]. In extragonadal germ cell tumours, a bilateral testicular biopsy is necessary. Weißbach [1] recommends performing the biopsy on the upper medial side of the testis. According to Skakkebaek [4] and Maase [5], TIN is diffusely distributed within the testicle, therefore, a single biopsy should be sufficient.

This case report demonstrates the limits of reliability of a single testicular biopsy for the detection of TIN. MRT showed clearly that the biopsy scar was only superficial and opposite the tumour.

We agree with Walz [6] that multiple biopsies increase the chances of diagnosing tumour or TIN, although a more thorough exploration of the testicle bears the great risk of complete loss of functioning testicular parenchyma. Most probably, TIN in the testicle is not diffuse but multifocal [7]. Therefore, a single testicular biopsy can give false negative results. Additionally, Hoeltl and colleagues [8] and Giwercman and colleagues [9] have shown that in patients with a testicular tumour, biopsy of the contralateral testicle does not exclude the development of an asynchronous contralateral tumour.

We conclude that, despite negative biopsies in patients with a contralateral testicular germ cell cancer and extragonadal germ cell tumours, a regular and careful examination of the testicles is mandatory.

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Vitiligo-like Lesions Following Immunotherapy With IFNα and IL-2 in Melanoma Patients

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SEVERAL FINDINGS support the concept of vitiligo as an autoimmune disease where destruction of melanocytes occurs. Most patients with active vitiligo have cytolytic anti-melanocyte antibodies [1–3]. The accumulation of activated T cells at the margins of the lesions has been demonstrated [4]. Vitiligo is associated with other autoimmune diseases such as primary hypothyroidism or type 1 diabetes mellitus [5, 6]. Thus, humoral and cellular immune mechanisms as well as a genetic predisposition may play a role in the disease's pathogenesis.

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An increased frequency of vitiligo in patients with metastatic melanoma has also been described by several authors (reviewed in [7]). The presence of vitiligo in melanoma patients has been shown to correlate with a better prognosis [8]. Recently, the development of vitiligo-like lesions in a high proportion of melanoma patients has been observed following combined polychemo- and immunotherapy with α-interferon (IFNα) and interleukin-2 (IL-2), but not with immunotherapy alone [9].

We have treated 65 patients with metastatic melanoma with IFNα and IL-2 without chemotherapy [10] and observed the development of vitiligo-like lesions in only 4 patients, all in areas of previous irradiation or following sunburns.

Patient 1

The patient was a 54-year-old Caucasian male. He received immunotherapy with IFNα (10×10^6 U/m^2 days 1–5) and continuous high-dose IL-2 (total of 3.75 mg/m^2 days 3–8; the treatment protocol is described in detail in [10]) because of large irresectable right axillary lymph node metastases, and had a partial response following four treatment cycles. Two and a half years before, right axillary lymph node metastases had already been successfully irradiated (50 Gy). Eight months following immunotherapy he again relapsed in the right axilla. He received another three cycles of immunotherapy, and had a partial response for 18 months. Following the second course of immunotherapy, he developed depigmentation for the first time starting in the area previously irradiated, but later progressively extending to involve non-irradiated skin areas.

Patient 2

The patient was a 22-year-old Caucasian male. Because of lymph node metastases, he had received irradiation of his right groin with 50 Gy, 2 months prior to immunotherapy. Following three cycles of immunotherapy (for schedule, see patient 1), he had a mixed response, with complete regression of lung metastases and stable disease of abdominal lymph node metastases. Following the second cycle, he developed a depigmentation of the skin in the irradiation field. Depigmentation progressed on the skin of both legs and the lower abdomen until death due to tumour progression 5 months later.

Patient 3

This patient was a 46-year-old Caucasian female. When she was referred, she presented with metastatic disease in mediastinal and axilliary lymph nodes. She received a total of five treatment cycles with IFNα and IL-2 (for schedule, see patient 1), and a partial remission was achieved. Residual mediastinal and axillary lesions were surgically removed, and the patient has now been in remission for 30+ months. Following the third treatment cycle, she presented with a hypopigmented area on the dorsum of both hands, where she reported she had a non-blistering sunburn 4 weeks earlier. This area is still progressing 2½ years later, now involving both forearms. Interestingly, this patient had also developed a severe polyarthritis resembling rheumatoid arthritis lasting for several months following immunotherapy.

Patient 4

This patient was a 53-year-old Caucasian female. She received a total of four treatment cycles with IFNα and IL-2 (for schedule, see patient 1), and had stable disease in a large para-aortic lymph node metastasis, which was then surgically resected. Histology revealed profound necrosis and fibrosis. She has now been without evidence of tumour for 10+ months. Following the last treatment cycle, she presented with hypopigmentation on the dorsum of both hands, forearms and shoulders, which is slowly extending. Like patient 3, she had a non-blistering sunburn in these areas several weeks earlier.

We report here on 4 of 65 melanoma patients who developed vitiligo-like depigmentation following treatment with IFNα and IL-2. Vitiligo-like lesions have recently been described to occur in a high proportion (61%) of patients receiving polychemotherapy together with immunotherapy, but not in those receiving chemotherapy or immunotherapy alone [9]. A case has also been reported of a patient developing vitiligo-like lesions and scleroderma following intralymphatic immunotherapy with irradiated melanoma cells [11].

In our cohort of patients, we observed the development of vitiligo-like lesions only in patients who had previously been irradiated or had a sunburn following immunotherapy. In all 4 patients, depigmentation started in the radiation field or the area of sunburn, and progressed after cessation of immunotherapy. All patients had evidence of tumour response.

In patients responding to immunotherapy, the same mechanisms may mediate both regression of melanoma cells and development of vitiligo. Based on the concept that normal self proteins can function as tumour antigens [12], specific cytotoxic T cells and antibodies may be able to recognise both melanocytes and melanoma cells. Several findings support this hypothesis: vitiligo auto-antibodies directed against melanocytes are also cytotoxic for melanoma cell lines [13]. Peptides derived from the melanocyte lineage-specific enzyme tyrosinase have recently been demonstrated to be a target of cytotoxic T cells in melanoma [14]. Monoclonal antibodies directed against tyrosinase and a tyrosinase-related protein were shown to react with human melanocytes and melanoma cells [15,16].

We observed the development of a vitiligo-like depigmentation only in areas of skin exposed to radiation prior to or during immunotherapy. One can speculate about the possible effects of radiation, which may lead to an increased immunogenicity of activated melanocytes or an enhanced influx of T cells or antibodies. Expression of HLA class II, as well as upregulation of ICAM-1, has been shown in melanocytes from skin affected by vitiligo, but not from normal skin or the lesions of psoriasis [17]. In none of the other 61 patients, including another 15 patients with complete or partial response, could we observe the development of depigmentation, suggesting that normal or resting melanocytes are usually not recognised by a melanoma-directed immune response. This observation is of importance when considering specific immunotherapeutic approaches in melanoma patients using melanocyte lineage-specific antigens.

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