REPORT

High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody

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Cancer can occur in patients with inflammatory myopathies. This association is mainly observed in dermatomyositis, and myositis-specific antibodies have allowed us to delineate patients at an increased risk. Malignancy is also reported in patients with necrotizing autoimmune myopathies, but the risk remains elusive. Anti-signal recognition particle or anti-HMGCR antibodies have been specifically associated with necrotizing autoimmune myopathies. We aimed at screening the incidence of cancer in necrotizing autoimmune myopathies. A group of patients (n = 115) with necrotizing autoimmune myopathies with or without myositis-specific antibodies was analysed. Malignancy occurred more frequently in seronegative necrotizing autoimmune myopathies patients and in HMGCR-positive patients compared to anti-signal recognition particle positive patients. Synchronous malignancy was diagnosed in 21.4% and 11.5% of cases, respectively, and incidence of cancer was higher compared to the general population in both groups. No specific type of cancer was predominant. Patients suffering from a synchronous cancer had a decreased median survival time. Cancer screening is necessary in seronegative necrotizing autoimmune myopathies and in HMGCR-positive patients but not in anti-signal recognition particle-positive patients.

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Introduction

Cancer is a major cause of mortality in idiopathic inflammatory myopathies (Torres et al., 2006). Cancer occurs in 20% of cases and this association is considered not to be fortuitous when it occurs within 3 years, before or after, the diagnosis of idiopathic inflammatory myopathies (Zahr and Baer, 2011). Identifying patients with high risk is thus crucial.

This association is mainly reported during dermatomyositis (Zahr and Baer, 2011). It has been shown that patients with dermatomyositis positive for either anti-transcriptional intermediary factor 1γ (Trallero-Araguás et al., 2012) or anti-nuclear matrix protein 2 (Fiorentino et al., 2013) antibodies have an increased risk of malignancy, underscoring the relevance of searching for myositis-specific antibodies as a part of cancer screening.

Previous case reports or case series have described cancer-associated myositis in the group of necrotizing autoimmune myopathies, but to date this link remains elusive (Levin et al., 1998; Vu et al., 2011). Definition of necrotizing autoimmune myopathy is based on pathological features following the European Neuromuscular Centre (ENMC) criteria (Hoogendijk et al., 2004). Necrotizing autoimmune myopathies are clinically characterized by muscle weakness of limb girdle muscles, whereas extraskeletal involvement is usually mild or absent (Allenbach and Benveniste, 2013). Two specific antibodies are strongly associated with necrotizing autoimmune myopathies: anti-signal recognition particle (SRP) (Miller et al., 2002) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) (Mammen et al., 2011; Allenbach et al., 2014), but most cancers associated with necrotizing autoimmune myopathies have been reported prior to their routine detection. In this study, we aimed to analyse the risk of cancer in a large cohort of patients with necrotizing autoimmune myopathy with or without myositis-specific antibodies.

Patients and methods

This is a long-term French observational multicentre patient study. Three groups of patients with necrotizing autoimmune myopathies were analysed: anti-SRP antibody-positive (anti-SRP+) patients, anti-HMGCR-positive (anti-HMGCR+) patients, and patients without any myositis-specific antibodies (MSA– patients).

Anti-SRP+ and anti-HMGCR+ patients with muscle weakness, increased creatine kinase levels and necrotic fibres on muscle biopsy were enrolled.

Anti-HMGCR and SRP antibodies were detected as previously described (Drouot et al., 2014). MSA– patients were defined as patients with necrotizing autoimmune myopathies based on ENMC criteria (Hoogendijk et al., 2004) and diagnosed negative for myositis-specific antibodies. The following myositis-specific antibodies were tested: anti-HMGCR (Drouot et al., 2014), anti-SRP, anti-Jo1 (D-Tek SA), anti-PL7 (D-Tek SA), anti-PL12 (D-Tek SA), anti-Mi2 (D-Tek SA) and anti-melanoma differentiation-associated gene 5 (D-Tek SA), anti-nuclear matrix protein 2 (EUROIMMUN,) and anti-transcriptional intermediary factor 1γ (EUROIMMUN).

All anti-SRP+ and anti-HMGCR+ patients diagnosed between 2000 and 2014 at the ‘Centre National de Reference de Pathologie Neuromusculaire Paris-Est’ of the Pitié-Salpêtrière Hospital were enrolled. In addition, anti-HMGCR+ patients diagnosed between 2005 and 2013 in eight university hospitals and four regional hospitals, were included. Finally, MSA– patients, diagnosed between 2008 and 2014 at the ‘Centre National de Reference de Pathologie Neuromusculaire Paris-Est’ of the Pitié-Salpêtrière Hospital, were included.

For each included patient, demographic data (age and sex), characteristics of the muscle disease [date of the first symptom, muscle strength evaluation using manual muscle testing according to the Medical Research Council (MRC) scale, and creatine kinase level], statin exposure and characteristics of treatments received by the patients, were recorded. The date of diagnosis of necrotizing autoimmune myopathy was defined as the date of the first muscle biopsy. The presence of cancer (date of diagnosis, topography, type and staging) was also collected. Cancer was considered as synchronous to the diagnosis of the myopathy if it occurred within 3 years, either before or after, the diagnosis of necrotizing autoimmune myopathy (Troyanov et al., 2005).

Approvals for this study were obtained from the Ministry of Higher Education and the Research (by submission to the ‘Advisory Committee on information processing for Research’ [Comité consultatif sur le traitement de l’information en matière de recherche (C.C.T.I.R.S.)]. The study was declared to the National Commission on Informatics and Liberties (CNIL) according to French regulatory requirements. It was approved by the local Ethics committee Ile-de-France VI Groupe Hospitalier Pitié Salpetrière.

Statistics analysis

Categorical variables are reported as numbers and/or percentages and were compared using Fisher’s exact tests. Quantitative variables are reported as mean [± standard
deviation (SD) and compared using Mann-Whitney tests or Kruskall-Wallis tests. A P-value < 0.05 was considered as significant. Survival was estimated using Kaplan-Meier curves; results were compared using Log-rank tests. Graphpad Prism version 6.00 Software (La Jolla, California, USA) was used for analysis.

Occurrence of malignancy was studied by calculating the standardized incidence ratio within 3 years, either before or after, the diagnosis of myopathy. Numbers of malignancy cases observed during the 6 years around myopathy diagnosis were compared to the number of malignancy cases expected to occur during this period if the risk was that of the general population sharing the same age and gender structure. Data on the incidence of malignancy in the general population were obtained from the Association of the French Cancer Registries (FRANCIM), which gathers data from 20 population-based regional French cancer registries.

Each patient accounted for 6 person-years around the diagnosis of myopathy, except patients who died or were diagnosed with malignancy and who were censored at the time of death or malignancy diagnosis. Patients with a diagnosis of cancer occurring >3 years after the onset of myopathy were censored and accounted for 6 person-years. Patients with a diagnosis of cancer occurring >3 years prior to myopathy were excluded from the standardized incidence ratios analysis. The expected number of cases of cancers was obtained by multiplying the patient-years at risk in each 5-year age group by the corresponding sex- and age-specific incidence rate. The observed number of incident cases of cancers was divided by the expected number to obtain the standardized incidence ratio estimate. Confidence intervals for standardized incidence ratios were calculated with an exact method based on the Poisson distribution, which is appropriate for cohort analysis when outcome is an uncommon event.

### Results

#### Patients’ characteristics

One hundred and fifteen patients were included (MSA− patients: n = 14; anti-HMGCR + patients: n = 52 and anti-SRP + patients: n = 49). The demographic characteristics, muscle involvement, statin exposure, skin and lung manifestations and the mean follow-up are shown in Table 1. Results of muscle biopsies of MSA− patients are shown in Supplementary Table 1. Few statistical differences were observed between the three groups. Muscle strength was lower in anti-SRP + patients. Statin exposure was more frequently observed in anti-HMGCR + patients.

#### Increased frequency of cancer associated with myopathy in MSA− and anti-HMGCR + patients compared to anti-SRP + patients

Malignancy occurred in 28.6% of MSA− patients, 17.3% of anti-HMGCR + and 8.1% of anti-SRP + patients. Mean age at the diagnosis of cancer was 73 ± 6 years in MSA−, 67 ± 15 years in anti-HMGCR +, and 68 ± 10 years in anti-SRP + patients. Only one case of cancer occurred before the age of 50 years (Table 1). The mean duration between the diagnosis of cancer and the myopathy was 1.2 ± 2.6 years in MSA−, 4.2 ± 4.9 years in anti-HMGCR +, and 6.7 ± 6.3 years in anti-SRP + patients. Three-quarters of malignancies occurred within 3 years of or before the diagnosis of MSA− myopathy, two-thirds in anti-HMGCR + patients, and one-half in anti-SRP + patients (Table 2). No specific type of cancer was observed (Table 2).

#### Increased risk of malignancy in MSA− and anti-HMGCR + patients compared to the general population

To determine if the risk of cancer was increased in patients with necrotizing autoimmune myopathies, we compared the results we obtained to the general age- and sex-matched population (Fig. 1).

MSA− patients have significantly increased standardized incidence ratios 8.35 (1.68–24.41) (P < 0.01). In addition, a significant increase is also observed in anti-HMGCR + patients: 2.79 (1.02–6.07) (P = 0.02); however, the standardized incidence ratio is less important. Conversely, no increased risk was observed in anti-SRP + patients, 1.65 (0.19–5.97) (P = 0.79). Data are presented in Fig. 1.
Poorer prognosis in patients with cancer

During the follow-up, seven patients died: two MSA– patients (14.2%), three anti-HMGCR + patients (5.7%), and two anti-SRP + (4%). Among these, five suffered from a synchronous malignancy. For the two remaining patients, one anti-SRP + patient died at the age of 27 from an unknown cause, and one anti-HMGCR + patient died from terminal cardiac insufficiency.

Depending on the serological status, survival was significantly different (Supplementary Fig. 1A). MSA– patients had a lower survival rate ($P = 0.047$). In addition, median survival of cancer associated with myositis was significantly decreased when compared to patients without malignancy (57.2 years, $P < 0.0001$) (Supplementary Fig. 1B).

Discussion

In this cohort of necrotizing autoimmune myopathies, we have observed an increased incidence of cancer in MSA– and anti-HMGCR + patients, but not in anti-SRP + patients. In both groups, malignancy occurred mainly after the age of 50, and mostly within 3 years of the diagnosis of necrotizing autoimmune myopathy.

This is the first time that malignancy has been analysed in a large cohort of necrotizing autoimmune myopathies, combining MSA +, anti-HMGCR + or anti-SRP +, and MSA– patients. This study shows that MSA– patients have a very high risk of malignancy. Despite the caution needed due to the small number of cases, evidence for a high risk of cancer is strengthened by large differences in standardized incidence ratios between the subgroups of patients and by the strong statistical significance of standardized incidence ratios. The risk is similar to that previously reported in anti-transcription intermediary factor 1 + positive dermatomyositis patients. Therefore, dermatomyositis can no longer be considered as the main idiopathic inflammatory myopathy with an increased risk of cancer. Of note, none of the MSA– patients fulfilled the criteria for

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Age at diagnosis of cancer (years)</th>
<th>Sex</th>
<th>Time between myopathy and cancer diagnosis (years)</th>
<th>Type of cancer</th>
<th>Tumour extension</th>
<th>Survival</th>
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</thead>
<tbody>
<tr>
<td>HMGCR</td>
<td>81</td>
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<td>−1.1</td>
<td>Lung carcinoma</td>
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<tr>
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<td>6.4</td>
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<tr>
<td>HMGCR</td>
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<td>M</td>
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<tr>
<td>SRP</td>
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<td>M</td>
<td>−1.7</td>
<td>Hepatocellular carcinoma</td>
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<td>Dead</td>
</tr>
<tr>
<td>SRP</td>
<td>73</td>
<td>F</td>
<td>1</td>
<td>Breast carcinoma</td>
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<tr>
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<td>M</td>
<td>10.2</td>
<td>Bladder carcinoma</td>
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<td>Alive</td>
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<tr>
<td>MSA–</td>
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<td>MSA–</td>
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<td>Dead</td>
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<tr>
<td>MSA–</td>
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<td>M</td>
<td>0.4</td>
<td>Gastric carcinoma</td>
<td>Metastatic</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Figure 1 Risk of cancer in patients with immune-mediated necrotizing myopathy compared to the general population. Risk of malignancy was measured using standardized incidence ratio (SIR) 3 years before or after the diagnosis of myopathy and compared to the general population of the same age and gender structure. Values for the anti-SRP +, anti-HMGCR +, and MSA– patients are represented with 95% confidence interval (CI). An increased risk of cancer was observed in MSA– and HMGCR + patients ($P < 0.01$ and $P = 0.02$, respectively).
dermatomyositis diagnosis and none of these patients harboured antibodies previously associated with cancer.

We also show, for the first time, that anti-HMGCR antibodies are associated with an increased risk of cancer, in line with previous data showing a trend towards increased incidence of malignancy (Limaye et al., 2014). The association between HMGCR antibody and cancer suggests that the anti-tumour immune response may be involved in autoimmune processes, as recently outlined in other autoimmune settings (Joseph et al., 2014).

In line with previous data in dermatomyositis patients, our results show the usefulness of myositis-specific antibodies in identifying subgroups of patients at an increased risk of cancer. Similarly to cancer associated with dermatomyositis patients (Zahr and Baer, 2011), synchronous cancer in necrotizing autoimmune myopathies occurred mainly after the age of 50 years, suggesting that cancer screening should be proposed to this specific subgroup of patients. In addition, as for patients with dermatomyositis (Hill et al., 2001; Antiochos et al., 2009), the majority of cancers occurred within 3 years of myopathy diagnosis, with an increased standardized index ratio for this period. However, as no predominant type of malignancy was observed in association with necrotizing autoimmune myopathies, no specific cancer screening can be proposed. These results are in line with those previously reported in dermatomyositis (Zahr and Baer, 2011), synchronous cancers occurred within 3 years of myopathy diagnosis, mainly after the age of 50 years, suggesting that cancer screening should be proposed to this specific subgroup of patients. In addition, as for patients with dermatomyositis (Hill et al., 2001; Antiochos et al., 2009), the majority of cancers occurred within 3 years of myopathy diagnosis, with an increased standardized index ratio for this period. However, as no predominant type of malignancy was observed in association with necrotizing autoimmune myopathies, no specific cancer screening can be proposed. These results are in line with those previously reported in dermatomyositis (Zahr and Baer, 2011). In addition, it was not possible to identify other factors associated with cancer due to the limited power of the study.

Data indicate that cancer should be carefully screened in patients with necrotizing autoimmune myopathies without myositis-specific antibody or with anti-HMGCR antibodies, older than 50 years, within 3 years of diagnosis, as such patients have an increased risk of cancer and a poorer prognosis.

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**Supplementary material**

Supplementary material is available at *Brain* online.

**References**


