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Review

Clinico-pathological characteristics of different types of immunodeficiency-associated smooth muscle tumours

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Abstract Rare Epstein–Barr virus (EBV)+ smooth muscle tumours (SMT) manifest typically under immunosuppression. Three major subtypes are known: human immunodeficiency virus-associated (HIV-SMT), after transplantation (PTSMT) or associated with congenital immunodeficiency syndromes (CI-SMT).

So far, there are no analyses which compare the clinico-pathological characteristics of all three subtypes.

Case reports and case series on these three tumour types were collected (1990–2012). Meta-data analysis was performed for identification of similarities and differences.

A total of 73 HIV-SMT, 66 PTSMT and 9 CI-SMT were evaluated. There was a slight female predominance (55–67%). Children were affected nearly equally in HIV-SMT (33%) and PTSMT (35%), while all CI-SMT occurred in children. HIV-SMT manifested preferentially in the central nervous system, gut/liver, skin, lungs/larynx/pharynx and adrenal glands. PTSMT were predominantly found in the liver, lungs/larynx/pharynx, gut/spleen and brain. CI-SMT were often found in lungs/larynx, brain, liver, adrenal glands and spleen. Antecedent EBV+ lymphoproliferations manifested more often in PTSMT.

In all three tumour subtypes, survival analyses did not show any significant differences regarding surgical therapeutic approaches, the occurrence of multiple tumours, tumour size or sarcoma-like histological features. HIV-SMT had the poorest overall survival, which might be attributed to HIV-associated infectious complications.

1. Introduction

Patients who have a compromised immune system are generally prone to acquire viral, bacterial and fungal

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infections and to develop tumours. In some of these patients, particular viruses are associated with specific tumour types which are uncommon in immunocompetent individuals, e.g. herpes virus 8 (HHV8)-associated Kaposi-type angiosarcoma [1]. Hampered function of cellular and humoral immunity and dysregulation of inflammation-associated physiological reaction can be due to four major reasons: (i) infection with human immunodeficiency virus (HIV), a disease which affects millions of people on a worldwide scale; (ii) drug-induced acquired immunosuppression, in particular in the context of transplantation of solid organs and haematopoietic stem cells; (iii) a diversity of rare congenital immunodeficiency syndromes; and (iv) 'endogenous' immunosuppression in (very) old individuals, which is thought to be secondary to reduced amounts of haematopoietic stem cells and reduced production of serum proteins [2–5]. Most of these individuals are at risk of developing lymphomas, which are often caused by infection with Epstein–Barr virus (EBV), e.g. post-transplant lymphoproliferative diseases (PTLD). In contrast to lymphomas, immunodeficiency-associated smooth muscle tumours (SMT) are rare complications [6,7]. Until now, three different subtypes have been described which are related to HIV (HIV-SMT), transplantation (post-transplant smooth muscle tumours/PTSMT) and congenital immune defects (CI-SMT).

The pathobiology of these subtypes is poorly understood. The tumour progenitor cell is thought to be derived from an aberrant myogenous vascular wall cell, because some PTSMT and HIV-SMT have been found near cerebral veins and sinuses [6]; however, the exact origin is not known. Normal smooth muscle cells do not usually express the EBV receptor CD21 and it is not clear how the virus enters the cells [6]. Furthermore, some HIV-SMT are negative for EBV, which indicates that the virus is at least not the only driver of aberrant proliferation. The EBV protein late membrane protein 1 (LMP1) is not usually expressed in PTSMT but in some HIV-SMT. PTSMT and HIV-SMT have activated phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) signalling [7] and PTSMT show an increased expression of v-myc avian myelocytomatosis viral oncogene homolog (MYC) [6]. Recently, we showed that PTSMT have a microRNA expression profile which is related to smooth muscle differentiation but not EBV infection [8].

The exact frequency of tumour manifestation is not known, but is most likely <1–5% of each patient group, for HIV, transplantation or congenital defects. Due to the rarity of these tumours, mainly only case reports exist which cursorily compare similarities and differences of a given patient with other case reports. In order to provide a more general overview, we have previously re-evaluated a large number of case reports and small patient cohorts of PTSMT [6]. We found that the type of immunosuppressive regimen is not associated with tumour manifestation [6]. On the one hand, since the kidney is the most frequently transplanted organ, most PTSMT manifested in kidney-transplanted patients. On the other hand, PTSMT relatively rarely manifest in kidneys. PTSMT can be found at any anatomical site, but preferentially occur in the recipients' own liver (in non-liver/kidney and other organs transplanted patients) or in the donors' liver in liver transplanted patients. These tumours are late complications (median 48 months after transplantation, range 5–348 months) and early onset tumours (<12 months after transplantation) occur only in <5% of cases [6].

A systematic comparison of clinical presentation, histopathology, therapy and prognosis of all three immunosuppression-associated SMT subtypes is lacking so far. Therefore, in the present study, we collected detailed information from published data and performed a systematic meta-analysis.

2. Material and methods

2.1. Immunodeficiency-associated SMT cohort

We have previously collected data from a total of 68 EBV+ PTSMT cases including four of our own patients [6]. This cohort was further modified regarding underlying association with EBV and congenital immune defects. One hepatic PTSMT had been excluded in our previous analyses, because this tumour was not associated with EBV [9]; in the current analysis, this case was now included. Furthermore, all patients with congenital immune defects were classified as CI-SMT, irrespective of whether tumours manifested after bone marrow transplantation. Before, three CI-SMT had been grouped with PTSMT [6,10,11]. Otherwise, the CI-SMT group would have been too small for a reasonable re-evaluation. Therefore, the PTSMT group now comprised 66 and not 68 cases.

These data were compared with newly collected data, which were derived from a review of the literature on HIV-SMT and additional CI-SMT. Cases were selected from the Pubmed data base in an arbitrary time interval from 1990 to 2012 (PTSMT cases have been collected in the corresponding interval [6]). In addition, the data files of our tissue archive were screened for immunodeficiency-associated SMT; uterine leiomyomas in female patients were considered to be sporadic [12].

The local Ethics committee (MHH) has approved the retrospective evaluation.

2.2. Statistical evaluation

The following parameters were statistically compared: differences in gender between the three SMT subtypes, age at SMT manifestation, type of immunosuppressive regimen, site of tumour manifestation, additional lymphoproliferation, pathological tumour characteristics