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The embryonic stem cell factor UTF1 serves as a reliable diagnostic marker for germinomas

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Summary

The transcription factor OCT4 is an established diagnostic marker for central nervous system (CNS) germinoma. However, no data are available to date concerning the expression of its downstream target undifferentiated embryonic cell transcription factor 1 (UTF1) in CNS germ cell tumours. We examined 21 CNS germinomas and two mixed CNS germ cell tumours for UTF1 and the post-transcriptional regulator LIN28 immunohistochemical expression. We compared the profile to established diagnostic germinoma markers and to the expression in six testicular and four metastatic germ cell tumours as well as 150 CNS tumours of various backgrounds. We found UTF1 expression in 23 of 23 and LIN28 in 20 of 23 CNS germ cell tumours. The established germinoma markers cKIT (23/23), OCT4 (21/23) and placental alkaline phosphatase (PLAP) (19/21) were also frequently expressed in our cohort. In terms of signal intensity and frequency, UTF1 showed similar results as cKIT but staining was superior to OCT4, PLAP and LIN28. OCT4 was absent in all CNS metastases and haemangioblastomas, while UTF1 was weakly observed in two metastases. With a sensitivity of 100% and a specificity of 97% in the detection of CNS germinomas, UTF1 serves as a new reliable alternative in the diagnostic setting of CNS germ cell tumours.

Key words: CNS, germinoma, LIN28, OCT4, UTF1.

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INTRODUCTION

Germ cell tumours are the most common solid malignancies in males between 15 and 35 years. In the central nervous system (CNS) they are rare, but may show frequencies of up to 15% of paediatric brain tumours in some Asian countries[1] and are often divided into germinomatous and non-germinomatous tumours. Germinomas account for two-thirds of all CNS germ cell tumours. In their pure form they usually have a good prognosis with a 10-year survival rate of approximately 90%.[2] CNS germinomas do not benefit from partial or even gross total resection as compared to diagnostic tumour biopsy alone.[2] Representative biopsy is required to confirm the histological diagnosis and determine the treatment modality when of non-germinomatous components are present.[3,4] In the last few years several new markers have been introduced to determine the individual tumour components, most of which are related to proteins also expressed in primordial germ cells or gonocytes. One marker commonly used in the diagnostic setting of CNS germinomas is cKIT (CD117) which is expressed in the cytoplasm of neoplastic germ cells.[5] However, cKIT is also expressed in the majority of gastrointestinal stromal tumours (GISTs) and in a subset of leiomyosarcomas.[6] The POU-domain transcription factor OCT4 is expressed in normal and neoplastic embryonic stem and germ cells.[7,8] OCT4 together with Noxa is responsible for the high chemosensitivity of germ cell tumours by mediating apoptosis via p53 activation.[9] In the routine diagnostic setting of testicular germ cell tumours (GCT) and CNS germinomas, nuclear OCT4 immunohistochemistry seems to be more sensitive than placental alkaline phosphatase (PLAP) and more specific than cKIT.[10,11] The synergistic interaction of OCT4 with SOX2 regulates the transcription of UTF1, another coactivator observed in pluripotent embryonic stem cells.[12] UTF1 protein expression has been reported in testicular germ cell tumours and human adult testes.[13] Another potential target of OCT4 is LIN28, which has been recently reported in testicular germ cell tumours[14] and primary extragonadal germ cell tumours.[15] LIN28 mediates post-transcriptional expression in human embryonic stem cells,[16] and is involved in cancer cell proliferation.[17] LIN28 serves as a reprogramming factor and RNA-conserved binding protein.[18] In paediatric central nervous system primitive neuroectodermal tumours (CNS-PNET), LIN28 expression is associated with poor patient prognosis and ependymoblastoma-like morphology.[19] LIN28 is further considered a potential therapeutic target since LIN28 suppression reduces the metastatic potential of cancer cell lines by modulating MAPK and Myc signalling.[20] CNS germ cell tumours phenotypically closely resemble gonadal germ cell tumours, although some genes such as testis-specific protein Y-encoded (TSPY) are regulated differentially.[21] For this reason, new immunohistochemical markers for gonadal germ cell tumours should also be analysed independently in CNS germ cell tumours. Therefore, we examined the expression of UTF1 in intracranial (CNS) germinomas, germ cell tumours and brain metastases of different origin (carcinoma, melanoma, sarcoma and lymphoma) to test its suitability as an additional diagnostic marker and compared it with OCT4, LIN28, cKIT and PLAP expression.

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MATERIALS AND METHODS

Patient data

Archival biopsy samples with the diagnosis 'germinoma' or 'mixed germ cell tumour' were retrieved from the neuropathology departments in Tuebingen, Stuttgart, Frankfurt, Heidelberg and Marburg. In total 23 CNS germ cell tumours (18 male, 5 female; mean age 18 years, range 10–33 years) were analysed. Twenty-one cases were classified as pure germinomas, the remaining two cases were mixed malignant germ cell tumours with additional teratoma and yolk sac components. Six testicular germ cell tumours (all male; mean age 28 years, range 20–38 years) and four brain metastases of germ cell tumours (all male; mean age 28 years, range 25–30 years), served as controls. Epidemiological data on these cases are shown in Table 1. In addition, three tissue microarrays containing 1000 μm duplicate punches of 59 carcinoma, 28 melanoma and eight sarcoma CNS metastases from 94 patients (51 male, 43 female; mean age 58.7 years, range 21–86 years), eight CNS haemangioblastomas (4 male, 4 female; mean age 53 years, range 24–81 years) and 47 primary diffuse large B cell lymphomas (25 male, 22 female; mean age 64 years, range 13–84 years) were used for immunohistochemistry to obtain sensitivity and specificity. Autopsy cases were excluded from this study because of possible prolonged fixation times. Carcinoma samples consisted of 19 lung, 18 breast, five colorectal, six prostate, three renal cancer samples, in addition to single cases originating form liver, nose, ovary, thyroid gland and two cancers of unknown primary (CUP). Metastatic sarcoma cases included two liposarcomas, two leiomyosarcomas, one malignant peripheral nerve sheath tumour, one spindle cell sarcoma and three undifferentiated sarcomas.

The diagnostics were performed according to the WHO classification system for CNS germ cell tumours by experienced neuropathologists.[22]

Immunohistochemistry

Formalin fixed, paraffin embedded specimens were cut to 4 μm slides and deparaffinised. Immunohistochemical stainings were performed using mouse monoclonal anti-UTF1 (Millipore, USA; 1:200 dilution), mouse monoclonal anti-Oct4 (Abcam, UK; 1:500), rabbit polyclonal anti-cKIT (DakoCytomation, Denmark; 1:100), rabbit monoclonal anti-LIN28 (Cell Signaling, USA; 1:100), mouse monoclonal PLAP (Dako; 1:25) and rabbit monoclonal beta-hCG (Dako; 1:500) antibodies on the automated Benchmark immunohistochemistry system (Ventana Medical Systems, USA). Heat-induced antigen retrieval was performed with CC1 cell conditioning solution (Tris-based EDTA buffer, Ventana) for 30 min for UTF-1 and cKIT. Pretreatment was as follows: 24 min CC1 for Oct-4 and PLAP, 32 min CC1 for LIN28, and no pretreatment for beta-hCG. Visualisation of the specific antibody binding was achieved using the UltraView Universal DAB kit (Ventana). Human ependymoblastoma for LIN28, GIST for cKIT and placenta for beta-hCG and PLAP served as positive controls. Appropriate negative controls (omission of the first antibody) were processed in parallel with each batch of staining.

Staining evaluation

Only nuclear staining for UTF1 and OCT4 was evaluated. For LIN28, PLAP, AFP, beta-hCG and cKIT, cytoplasmatic staining of the tumour cells, independent of additional nuclear positivity was recorded. Tumours were considered positive when more than 5% of the tumour cells exhibited a detectable immunoreactivity. Nuclear and cytoplasmatic staining was semiquantitatively recorded as absent, weak, moderate and strong positive. Detailed analysis of the percentage of stained tumour cells was omitted for OCT4, CKIT and UTF-1 because in germ cell tumours the tumour cells stained uniformly positive for the antibodies analysed. For LIN28, tumours were classified as either incomplete staining when not all tumour cells were positive, or as complete staining when expression was observed in more than 95% of the tumour cells.

RESULTS

Detailed results of immunohistochemistry of germ cell tumours are shown in Table 1. A very strong nuclear OCT4 (if present)

Table 1 epidemiological data of samples immunostained for UTF1 immunohistochemistry

Case #	Sex	Age	Location	Diagnosis	UTF1	CKIT	OCT4	LIN28	PLAP
1	M	14	Pineal	Germinoma	+	+	+	+	+
2	M	16	3rd ventricle	Germinoma	+	+	+	+	+
3	F	13	3rd ventricle	Germinoma	+	+	+	+	+
4	M	16	Hypothalamus	Germinoma	+	+	+	−	NA
5	M	18	Pineal	Germinoma with syncytiotrophoblasts	+	+	+	+	+
6	F	12	Suprasellar	Germinoma	+	+	+	+	+
7	M	20	Pineal	Germinoma	+	+	−	−	NA
8	M	21	Intra/Suprasellar	Germinoma	+	+	+	+	+
9	M	15	Pineal, Sellar	Germinoma	+	+	+	+	+
10	M	23	Pineal	Germinoma	+	+	+	+	+
11	M	15	Hypophysis	Germinoma	+	+	+	+	+
12	M	19	Pineal	Germinoma	+	+	+	+	+
13	F	16	Sellar	Germinoma	+	+	+	+	+
14	M	23	Pineal	Germinoma	+	+	−	NA	+
15	M	33	3rd ventricle	Germinoma	+	+	+	+	+
16	F	11	Pineal	Germinoma	+	+	+	+	+
17	M	20	Pineal	Germinoma with syncytiotrophoblasts	+	+	+	+	−
18	M	25	Pineal	Germinoma with syncytiotrophoblasts	+	+	+	+	+
19	M	13	Pineal	Germinoma	+	+	+	NA	−
20	M	16	Pineal	Germinoma	+	+	+	NA	+
21	F	10	Pineal	Germinoma with syncytiotrophoblasts	+	+	+	+	+
22	M	12	Pineal	Mixed germ cell tumour with teratoma, germinoma, yolk sac tumour and embryonal carcinoma	+	+	+	−	+
23	M	25	Pineal	Mixed germ cell tumour with teratoma, germinoma and yolk sac tumour	+	+	+	+	+
24	M	20	Testis	Seminoma	+	+	+	+	NA
25	M	38	Testis	Seminoma	+	+	+	+	−
26	M	22	Testis	Mixed germ cell tumour with seminoma and embryonal carcinoma	+	+	+	+	+
27	M	25	Testis	Seminoma	+	+	+	+	+
28	M	33	Testis	Seminoma	+	+	+	+	−
29	M	33	Testis	Seminoma	+	+	+	+	−
30	M	25	Frontal lobe	Yolk sac tumour metastasis	−	+	−	+	−
31	M	29	Parietal lobe	Embryonal carcinoma metastasis	+	+	+	+	+
32	M	30	Frontal lobe	Yolk sac tumour metastasis	−	+	−	+	−
33	M	29	Occipital lobe	Embryonal carcinoma metastasis	+	+	+	+	NA

F, female; M, male; NA, not enough tissue available.

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