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ORIGINAL COMMUNICATION

Malignant tumors in autoimmune encephalitis with anti-NMDA receptor antibodies

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Abstract

Objective The aim of this study was to describe specificities of patients with NMDA receptor antibody (NMDAR-Ab) encephalitis associated with a malignant tumor.

Methods Retrospective observational study of 252 patients with NMDAR-Ab encephalitis of the French Paraneoplastic Neurological Syndrome Reference Center. Patients were classified in three groups: (1) non-malignant ovarian teratomas, (2) malignant ovarian teratomas (immature), and (3) other malignant tumors.

Results Sixty patients (23.8%) had an associated tumor and 15 (6%) were malignant. No particular neurological symptom was observed in these patients. Ovarian teratomas were the most frequent (51 cases) with 6 of them immature (11.8% of teratomas). Nine patients (3.6%) developed other malignant tumors (3 small cell lung carcinomas, 1 uterine adenocarcinoma, 1 prostate adenocarcinoma, 1 Hodgkin lymphoma, 1 pineal dysgerminoma, 1 neuroblastoma and 1 pancreatic neuroendocrine tumor). Among patients with a cancer other than teratoma, 6/9 were elderly patients (median age 65 years, representing 30% of elderly patients with such encephalitis) compared to a median age of 26 years in adult patients included herein. The clinical course was similar in the three groups, other than a higher death rate among patients with malignant tumors (86 versus 2%; $p < 0.001$) mainly due to tumor progression (5/7 deaths).

Conclusion Immature ovarian teratomas represent 11.8% of all teratomas in patients with NDMAR-Ab encephalitis. The other malignant tumors are mainly observed in elderly patients. The presence of a malignant tumor does not impact the neurological presentation but is directly associated with a higher risk of death.

Keywords NMDAR · Autoantibodies · Encephalitis · Anti-NMDA receptor antibodies · Malignant tumors · Paraneoplastic syndrome

Introduction

Encephalitis with anti-NMDA receptor antibodies (NMDAR-Abs) is the most common type of autoimmune encephalitis [1]. It was initially described in 5 women with mature ovarian teratomas [2] and the target antigen, the GluN1 part of the NMDA receptor, was identified in 2007 [3]. Since then approximately 800 cases have been reported in the literature [4–7]. The disease usually occurs in young adult women although it can also affect adult male patients (10% of cases [8]) and children of both sexes (40% [9]). In the literature, approximately 30–40% of all affected patients have an associated underlying neoplasm, mostly mature ovarian teratoma, also known as dermoid cyst—the most common benign germ cell neoplasm [4, 5]. However, malignant tumors have been also described in around 5% of cases [4, 5, 10]. The aim of the present retrospective study was to describe the clinical presentation and outcome of patients with NMDAR-Ab encephalitis and malignant tumor to identify potential neurological or oncological particularities.

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Methods

Patients

From October 2007 to May 2017, 280 patients were diagnosed with NMDAR-Ab encephalitis at the French Paraneoplastic Neurological Syndrome Reference Center. For a diagnosis of NMDAR-Ab encephalitis, the patient cerebrospinal-fluid (CSF) analysis had to fulfill the following previously established and now internationally recognized criteria for the presence of IgG-NMDAR-Abs: (1) specific pattern of neuropil immunostaining in the rat brain hippocampus, and (2) positive cell-based assay (CBA) using HEK293 cells expressing both the GluN1 and GluN2B subunits of the NMDAR [4, 7].

Clinical data collection

Detailed clinical information was obtained by the authors or provided by referring physicians. These data were collected by the French Paraneoplastic Neurological Syndrome Reference Center at the time of biological diagnosis and over the duration of patient follow-up.

Prodromal symptoms were defined as signs that occurred prior to the first neurological symptoms. They were divided in four groups: (1) headache, (2) gastrointestinal symptoms, (3) infection signs, and (4) other. Presenting symptoms were defined as first symptoms observed and reported by the patient or his/her entourage after the prodromal state. Subsequent symptoms were all new symptoms arising after the first ones, after at least 24 h. Symptoms were divided into six categories, as previously described and detailed [10]. We assessed the results from the first MRI and CSF findings. All patients were screened at least once for systemic tumor using MRI, thoracoabdominal tomodensitometry, abdominal and pelvic echography, or fluoro-2-deoxy-D-glucose body-PET. When a malignant tumor was diagnosed, the stage at diagnosis was collected. Encephalitis and cancer treatment modalities and their sequence were detailed for each patient. Neurological outcome was assessed with the modified Rankin scale (mRS). mRS Score was determined at diagnosis of the disease and recovery was defined by a mRS Score between 0 and 1.

GluN1 Immunohistochemical detection on malignant tumors

When a paraffin-embedded tumor sample was available, four-micrometer-thick sections were cut and immunostained using a commercial antibody directed against the GluN1 (clone R1JHL, Thermo-Fisher, Huntsville, AL, USA) to detect tumor cell expression of the NMDAR.

Sections (4 µm) of paraffin embedded specimens were deparaffinized and saturated (in PBS 0.1M with BSA 1%, and Triton X-100 0.3%), tumor samples were incubated with anti-GluN1 antibody at 1.5 µg/mL, overnight at 4 °C (diluted in PBS with 5% goat serum). After applying secondary biotinylated antibody against mouse immunoglobulins (1.6 µg/ml, Jackson, UK), labeling was developed with the avidin-biotin-peroxidase method (PK6100, ABC HRP kit, Vectastain, CA, USA). Results were photographed under a microscope using Zeiss Axiovision software (Zeiss, Thornwood, NY, USA).

Statistical analysis

Statistical analyses were performed using R software, with a Fisher's exact test.

Results

Medical records of 280 patients with NMDAR-Ab encephalitis were available in the French database. We excluded 28 cases for which data were lacking, mainly foreign patients. The cohort of 252 patients (median age 21 years, range 1–76) included 94 children (median age 11 years, range 1–18; 65 girls and 29 boys), 130 adult women (51.6%, median age 26 years, range 18–76), and 28 adult men (11% median age 26 years, range 18–76). A tumor was reported in the clinical record of 64/252 patients, corresponding to 25.3% of the cohort (57 females, 5 men, 2 little boys).

According to neurological paraneoplastic syndrome (PNS) guidelines, only tumors diagnosed within 2 years before or after the encephalitis diagnosis were considered [1]. Among the 60 remaining patients with an associated tumor, 45 had a mature ovarian teratoma, 6 an immature ovarian teratoma, and 9 a malignant tumor of another histological type [small cell lung cancer ($n=3$), Hodgkin lymphoma ($n=1$), uterine adenocarcinoma ($n=1$), prostate adenocarcinoma ($n=1$), pineal dysgerminoma ($n=1$), neuroblastoma ($n=1$), and pancreatic neuroendocrine tumor ($n=1$)]. Detailed clinical data of these patients are presented in Table 1.

Immature ovarian teratomas

An immature ovarian teratoma was diagnosed in 6 female patients (patients 1–6, Table 1), who were aged between 12 and 38 years (median age 22 years; Table 2). Among the 169 pubescent females included in the cohort (older than 12 years old), 45 (26.6%) had a mature ovarian teratoma and

Table 1 Clinical features, treatment and outcome of our patients with malignant tumors

Case no.	Sex, age (year)	Presenting symptoms	Subsequent symptoms	CSF	Tumor type (stage), delay between 1st symptoms and tumor diagnosis	1st brain MRI	Treatment	Outcome
1	F, 35	Anterograde amnesia	Anterograde amnesia Behavioral disturbances Seizures Aphasia Attention disorders mRS = 5	Cells: 9 Prot: 0.7 OB: absence	Immature ovarian teratoma (1A grade 3) 1 month	Normal	IV Ig Methylprednisolone Surgery Chemotherapy	mRS = 0 at 6 months Still alive at 10 years
2	F, 20	Headache Psychotic and behavioural disturbances	Anterograde amnesia Behavioral disturbances, Seizures Orofacial dyskinesia Dysautonomia mRS = 5	Cells: 64 Prot: < 0.3 OB: NA	Immature ovarian teratoma (1A grade 1) 20 days	Normal	IV Ig Methylprednisolone Rituximab Surgery Azathioprine	mRS = 1 at 24 months Still alive at 4.5 years
3	F, 38	Headache Confusion	Anterograde amnesia Behavioral disturbances Seizures Orofacial dyskinesia Dysautonomia mRS = 5	Cells: 143 Prot: 0.76 OB: NA	Immature ovarian teratoma (1A grade 2) 4 months	Normal	IV Ig Plasmapheresis Surgery Chemotherapy	Tumor relapse at 3 months mRS = 3 at 24 months Still alive at 10 years
4	F, 19	Confusion Aphasia Behavioral disturbances	Orofacial dyskinesia, Dysautonomia Loss of consciousness Confusion Anterograde amnesia Aphasia mRS = 5	Cells: 200 Prot: < 0.3 OB: NA	Immature ovarian teratoma (1A grade 2) 6 days	Normal	Surgery Chemotherapy Methylprednisolone IV Ig Cyclophosphamide	mRS = 1 at 3 months Still alive at 4 years
5	F, 23	Delirium	Behavioral disturbances Anterograde amnesia Seizures mRS = 4	Cells: 3 Prot: 0.32 OB: NA	Immature ovarian teratoma (1A grade 1) 41 days	Normal	IV Ig Methylprednisolone Surgery	mRS = 0 at 8 months Still alive at 3.5 years
6	F, 12	Confusion Delirium	Oral dyskinesia Seizures Dysautonomia mRS = 5	Cells: 0 Prot: < 0.4 OB: NA	Immature ovarian teratoma (1A grade 2) 6 days	Normal	Surgery Chemotherapy Immunoadsorption Methylprednisolone Plasmapheresis Rituximab	mRS = 0 at 6 months Still alive at 21 months

Table 1 (continued)

Case no.	Sex, age (year)	Presenting symptoms	Subsequent symptoms	CSF	Tumor type (stage), delay between 1st symptoms and tumor diagnosis	1st brain MRI	Treatment	Outcome
7	F, 67	Behavioural disturbances Memory impairment Fever	Loss of consciousness Confusion Orofacial dyskinesia Behavioral disturbances Dysautonomia Memory impairment Aphasia mRS = 5	Cells: 90 Prot: 0.73 OB: NA	SCLC (TXN3M0) 8.8 months	Bilateral Hi HS	Methylprednisolone, Plasmapheresis Chemotherapy Radiotherapy Rituximab	mRS = 1 at 9 months Tumor recurrence at 21 months Death at 36 months after tumor progression
8	M, 66	Partial and generalized seizures Memory impairment Confusion Language impairment	Seizures Anterograde amnesia Confusion Aphasia Loss of consciousness mRS = 5	Cells: 21 Prot: 0.58 OB: Yes	SCLC (T0N3M0) 21 days	Bilateral Hi HS	Methylprednisolone IgIV Plasmapheresis Chemotherapy	mRS = 5 at 1 month Death of tumor progression 1 month after onset
9	F, 62	Mood disorder	Dysautonomia Loss of consciousness Aphasia Seizures Orofacial dyskinesia Behavioral disturbances Memory impairment mRS = 5	Cells:6 Prot: > 0.4 OB: NA	SCLC (T2BN0M1) 25 days	Bilateral Hi HS	Methylprednisolone IV Ig Chemotherapy Rituximab	mRS = 5 at 1 month Death of tumor progression 2 months after onset
10	M, 25	Psychotic disorder, Seizures Confusion	Anterograde amnesia Behavioral disturbances Orofacial dyskinesia Loss of consciousness Aphasia mRS = 5	Cells: 25 Prot:0.57 OB: NA	Hodgkin (Ann Harbor II) 1.5 months	Normal	IV Ig Chemotherapy	Total remission mRS = 4 at 6 months Unexplained sudden death 8 months after onset
11	F, 71	Cognitive disorder Behavioral disturbances	Confusion Seizures Orofacial dyskinesias Psychiatric disorder (hallucinations) mRS = 4	Cells: 5 Prot: < 0.4 OB: NA	Uterin Adenocarcinoma (pT3bN1) Tumor discovered 5 months before	Normal	Surgery Chemotherapy IV Ig Methylprednisolone Cyclophosphamide	mRS = 2 at 7 months Tumor metastasis at 6 months Death of tumor progression18 months after onset

Table 1 (continued)

Case no.	Sex, age (year)	Presenting symptoms	Subsequent symptoms	CSF	Tumor type (stage), delay between 1st symptoms and tumor diagnosis	1st brain MRI	Treatment	Outcome
12	F, 50	Behavioral disturbances Fever	Cognitive disorder Seizures Confusion Mutism Abnormal movement Catatonia mRS = 5	Cells: 43 Prot: 0.43 OB: NA	Pancreas neuro endocrine tumor (Afasaniev et al.) (T2N0M0) 4 months	Normal	Methylprednisolone IVIg Rituximab Surgery	mRS = 0 at 24 months Still alive at 30 months
13	M, 64	Fever Sub-acute cerebellar ataxia	Cerebellar ataxia Cognitive disorder Abnormal movement mRS = 3	Cells: 20 Prot: NA OB:NA	Prostatic Adenocarcinoma (T1cN0M0) 1.5 months	Normal	Hormonotherapy IgIV Methylprednisolone Rituximab	mRS = 4 at 6 months Death of infectious meningitis 6,5 months after onset
14	M, 9	Behavioural disturbances, Sleeping disorders Anorexia	Dystonia oral dyskinesia Sleeping disorders Left extrapyramidal syndrome Autism Encopresis Dysautonomia Seizures mRS = 4	Cells: 0 Prot: 0.43 OB: NA	Pineal dysgerminoma (NA) Tumor discovered 9 months before encephalitis onset	Hydrocephaly, Heterogeneous Pineal tumor	Surgery Radiotherapy Chemotherapy IV Ig Rituximab Cyclophosphamide	mRS = 0 at 24 months Still alive at 34 months
15	M, 3	Fever Vomiting Seizures	Seizures Choreo-Dystonia Oral dyskinesia Loss of consciousness Dysautonomia mRS = 5	Cells: 7 Prot: < 0.40 OB: NA	Neuroblastoma (Lebas et al. 2010) (Stage 4 (INSS)) 2 months	Moderate hydrocephaly HS cerebellum T1 T2	Surgery Chemotherapy, plasmapheresis	mRS = 5 at 9 months No tumor reponse Death 10 months after onset due to tumor progression

Units: Cells: number/ mm^3, Proteinorachia: g/L

F female, *M* male, *SCLC* small-cell lung carcinoma, *CSF* cerebrospinal fluid, *Prot* proteinorachia, *OB* oligoclonal bands, *MRI* magnetic resonance imaging, *IVIg* intravenous immunoglobulins, *mRS* modified Rankin score, *Hi* hippocampus, *HS* hypersignal on T2 FLAIR, *NA* not available

Table 2 Comparison of the clinical presentation of patients with an associated tumor

	Mature ovarian teratomas ($n=44$)	Immature ovarian teratomas ($n=6$)	Malignant tumors in adults ($n=7$)	Malignant tumors in children ($n=2$)	*p*value
Median age, years (range)	25 (15–45)	22 (12–38)	65 (25–71)	6 (3–9)	
Median interval between diagnosis of encephalitis to tumor, days (range)	7 (−26–643)	0 (−6–131)	2 (−244–238)	−283 and −2359	NS
First symptoms, *n* (%)					
Behavioral and psychiatric features	36 (82)	5 (83)	5 (71)	1	NS
Seizure	4 (9)	0	2 (28)	1	NS
Cognitive dysfunction	13 (30)	3 (50)	4 (57)	0	NS
Movement disorders	5 (11)	1 (17)	0	1	NS
Dysautonomia	1 (2)	0	0	0	NS
Subsequent symptoms, *n* (%)					
Behavioral and psychiatric features	36 (82)	5 (83)	5 (71)	1	NS
Seizure	27 (61)	5 (83)	4 (57)	2	NS
Cognitive dysfunction	44 (100)	6 (100)	7 (100)	2	NS
Movement disorders	35 (80)	4 (67)	6 (86)	2	NS
Dysautonomia	33 (75)	4 (67)	3 (43)	2	NS
Median follow-up time, months (range)	18 (1–24)	24 (1–24)	9 (3–24)	6 and 9	NS
mRS, *n* (range) [assessable cases]					
Median mRS at diagnosis	5 (4–5) [43]	5 (4–5) [6]	5 (2–5) [7]	4 and 5 [2]	NS
Median mRS at 3 months	4 (1–5) [39]	3 (0–5) [5]	3 (0–6) [7]	2 and 5 [2]	NS
Median mRS at 6 months	2 (0–5) [37]	2 (0–5) [5]	2 (0–6) [5]	2 and 5 [2]	NS
Median mRS at 12 months	1 (0–5) [30]	1 (0–4) [4]	1 (0–6) [5]	6 [1]	NS
Median mRS at 24 months	0 (0–6) [16]	0 (0–3) [4]	0 (0–6) [6]	6 [1]	NS
Clinical severity, *n* (%)					
ICU	37 (84)	5 (83)	5 (71)	0	NS
Death	1 (2)	0	6 (86)	1 (50)	<0.0001

One patient with mature ovarian teratoma and one with Hodgkin lymphoma were excluded from analysis due to missing data

Fisher's exact test

ICU intensive care unit, *mRS* modified Rankin score, *NS* not significant

6 an immature ovarian teratoma representing 11.8% of all the ovarian teratomas in the cohort.

The 6 immature ovarian teratomas were unilateral with intact capsule (stage 1A). For one patient details on tumor treatment were not available. No adjuvant treatment was given to 2 patients with a low-grade immature teratoma (G1, patients 2 and 5). Adjuvant chemotherapy with three cycles of BEP (BEP: cisplatin, etoposide, bleomycin) was introduced after surgery for 2/3 patients (patients 4 and 1) with high-grade tumors (G2 and G3). In patient 3 (grade G2), the chemotherapy was introduced only after the detection of a recurrence 3 months later. After a median follow-up of 2 years, no tumor recurrence was reported in these patients.

No particular clinical or outcome specificity was observed in the 6 patients with an immature teratoma compared to 44 patients (one case with mature ovarian teratoma was excluded due to lack of information on clinical evolution.) with mature tumors and assessable details data (Tables 1, 2). The complete clinical pattern was severe in both groups; mRS was 5 at diagnosis in more than 80% of patients in both groups, requiring admission to an intensive care unit. The prognosis was good at 24 months; 75% complete recovery (3/4 assessable cases) among patients with immature teratoma (mRS 0–1) versus 94% (15/16 assessable cases) among patients with mature teratoma. A poor outcome was observed only in one patient (patient 3) with malignant teratoma despite a complete tumor remission with severe cognitive sequelae and a permanent total disability 5 years after diagnosis; poor outcome was also observed in one patient with a mature teratoma who died from lethal complication of long-lasting intensive care 24 months after the first symptoms.

Other malignant tumors in adult patients

A malignant tumor (other than teratoma) was diagnosed in 7 adult patients (4.4% of adult patients, 4 females and 3 males, median age 65 years, range 25–71; Table 1).

Among these patients, 6 were aged over 45 years and represented 31.6% of the 19 patients aged over 45 years included in the cohort. A small cell lung carcinoma (SCLC) was observed in three patients (62, 66, and 67 years of age), a Hodgkin lymphoma in one young man (25 years), a uterine adenocarcinoma in a 71-year-old woman, a pancreatic neuroendocrine tumor in a 50-year-old woman [11], and a prostatic adenocarcinoma in a 64-year-old man. All patients had no remarkable personal medical history (including history of autoimmune disease or immunosuppression). All but one cancer (the uterine adenocarcinoma diagnosed 5 months before encephalitis onset) was diagnosed after the onset of the NMDAR-Ab encephalitis. The clinical presentation of patients with malignant tumors did not differ from the others (Table 2) and the immunomodulatory treatments were also similar. The cancers were treated according to histological type and tumor staging (Table 1). After a median follow-up of 9 months (range 3–24), the outcome was unfavorable for most patients with malignant tumors. Only one patient survived; at the time of writing, she is in complete cancer remission without neurological symptoms (patient 12). Four patients died from tumor progression or infectious complication without neurological improvement despite immunomodulatory treatments (patients 8, 9, 11, and 13). Despite neurological improvement, patient 7 died 2.5 years after encephalitis onset of tumor progression. Patient 10 experienced complete tumor response and slowly improved neurologically, before he suddenly died from an unexplained cause 8 months after onset (Table 1).

Malignant tumors in children

Among the 94 children (aged under 18 years) included herein, 2 (2.1%) had a malignant tumor and both were under 12 years of age (3.7% of children aged under 12 years). A 9-year-old boy (patient 14) had a pineal germ cell tumor with mature teratoma cell component (consistent with the diagnosis of dysgerminoma), and a 3-year-old boy (patient 15) had a metastatic neuroblastoma [12] (Table 1). Patient 15, who had a neuroblastoma, was treated by chemotherapy leading to tumor remission. However, his oncological and neurological status gradually deteriorated and he died 10 months after the initial symptoms. Concerning patient 14, the pineal mass was diagnosed 9 months before NMDAR-Ab encephalitis onset and no tumor recurrence was observed concomitantly with the encephalitis. He received a first and a second-line of immunotherapy; at last known status the patient is free from tumor recurrence, but severe cognitive sequalae persisted (mRS 3 at 6 months).

GluN1 expression by malignant tumors

GluN1 NMDAR subunit expression was detected by immunohistochemistry in 5/8 of the analyzed samples of malignant tumors. The immature teratomas of patients 2 and 4, the pineal germ cell tumor (patient 14), the pancreatic neuroendocrine tumor (patient 12), and the prostate adenocarcinoma (patient 13) expressed GluN1 subunit of the NMDAR. No expression of NMDAR was detected in the analyzed samples of SCLC of the patient 7 and 8, or in the sample of Hodgkin lymphoma of patient 10 (Fig. 1).

Discussion

In the cohort presented herein, nearly a quarter of patients with NMDAR-Abs encephalitis had an underlying neoplasm, predominantly mature ovarian teratomas, as previously reported [5, 13, 14]. The vast majority of patients with an associated tumor were female, and these represented nearly a third of girls and women with NMDAR-Ab encephalitis. No ovarian teratoma was diagnosed in children younger than 12 years or adult females older than 38 years.

Immature teratoma was only observed in 6 patients, but these represented 11.8% of ovarian teratomas associated with NMDAR-Ab encephalitis, which is higher than the usual 3% observed in general cohort of ovarian teratoma [15–17]. International guidelines recommend specific adjuvant oncologic treatments according to the grading of immature teratomas [18]. The guidelines currently recommend that chemotherapy must be considered for patients with grade 2 tumors according to the circumstances. The recurrence, observed in the patient with grade 2 immature teratoma who did not received chemotherapy initially, underscores the need to systematically consider chemotherapy in these patients when the grade is greater than or equal to 2. However, we did not observe differences in clinical presentation or course between patients with mature or immature ovarian teratomas and no specific neurological treatment is required in these patients.

In addition to immature teratomas, 9 malignant tumors were detected in the cohort. Two malignant tumors were detected in children younger than 12 years of age, and the others in 7 adults older than 45 years. Interestingly, this last point is confirmed by a review of the literature since among the 22 described cases with NMDAR-Ab encephalitis and associated malignant tumors other than immature teratoma (Table 3), 17 (77%) patients were older than 45 years at diagnosis. Interestingly, 28 cases of NMDAR-Ab encephalitis older than 45 years have been published [5]; including the 19 additional cases reported herein, 12/47 (25.5%) developed a malignant tumor, suggesting that in older patients a cancer

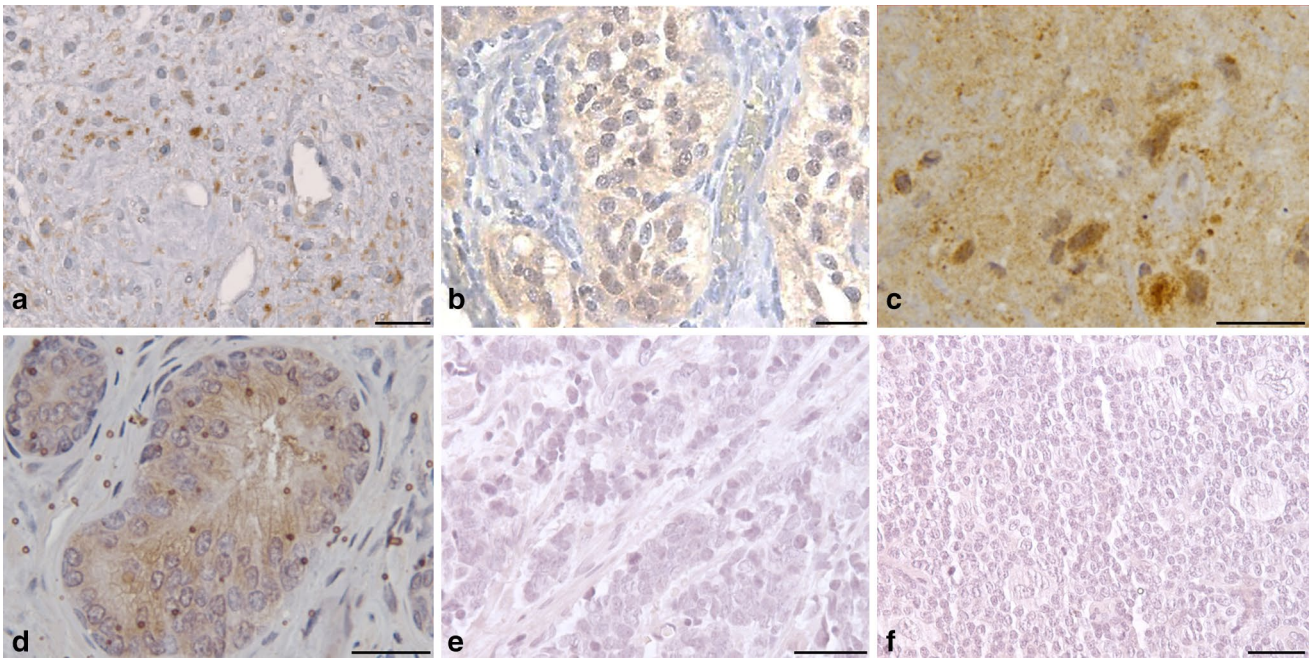

Fig. 1 GluN1 expression in malignant tumor associated with NMDAR-Ab encephalitis. GluN1 expression is detected by immunolabeling in a representative immature ovarian teratoma (**a**), in the pancreas neuroendocrine tumor (**b**), the pineal germ cell tumor (**c**) and the prostate adenocarcinoma (**d**). GluN1 expression is not detected in the SCLC sample (e) or in the Hodgkin lymphoma sample (**f**). Scale bar 50 µm for **a, b, e** and **f** and 80 µm for **c, d**

must be carefully searched for, as in classical paraneoplastic neurological syndromes.

In the present cohort, adult patients with malignant tumors had an unfavorable outcome; most had died at 24 months after diagnosis, while this was the case for only a minority of those with ovarian teratoma. This poor prognosis is clearly attributed to the oncological status of these patients, since most of them had an advanced tumor stage with metastases, and the neurological context is likely to burden the prognosis. Therefore, in clinical practice, even if associated malignant tumors are rare in NMDAR-Ab encephalitis (6% herein), these patients must be considered to have a poor prognosis and treated acutely. After 45 years of age, if no tumor is detected after a first screening, these investigations should probably be repeated over the subsequent months, as recommended for classical paraneoplastic neurological syndromes [28]. In children, particularly those aged under 12 years, tumors have been rarely reported [5] which does not incite systematic investigation for an underlying tumor in children.

As illustrated by the cases reported herein, malignant tumors associated with NMDAR-Ab encephalitis are very heterogeneous, ranging from Hodgkin lymphoma, to small cell lung or prostatic cancer. Among the 30 reported malignant tumors (including those described herein), most have a neuroendocrine differentiation or a germ cell origin (1 teratoma of the fallopian tube, 2 testicular tumors, and 4 neuroendocrine tumors; Table 3). Concerning the two reported children, their tumors were a germ cell tumor with neural component and a neuroblastoma which originates from the neural crest. They are, therefore, more likely to express neuronal proteins such as GluN1 NMDAR subunit, which was the case herein for 5/8 of malignant tumors and in a few cases reported in the literature [10, 22]. These observations and the possible rapid neurological improvement after tumor resection [5] suggest that a peripheral immune response against tumor autoantigens could be involved in the production of anti-NMDAR auto-antibodies.

Conclusion

Nearly a quarter of patients with NDMAR-Abs encephalitis had an associated tumor, mainly ovarian teratoma. In the latter, immature tumor is more frequent (11.8%) than the 3% described in the general cohort of ovarian teratoma and should be carefully searched for to be treated appropriately. Malignant tumors are exceptional before the age of 12 but are present in more than 25% of cases after 45 years of age and NMDAR-Ab encephalitis must be probably considered as paraneoplastic at this age.

Table 3 Review of malignant tumors found in the present cohort and in the literature

Type of tumor	Number of patients	Age of patients (years), sex	References
Small cell lung cancer	1	62, male	Coban et al. [19]
	1	60, female	Jeraiby et al. [20]
	3	62, 66, 67, 1 male, 2 females	Herein
Lung cancer	1	60, male	Wu [21]
	2	76, male, one NA	Titulaer et al. [5]
Breast tumor	2	NA, female	Titulaer et al. [5]
Ovarian carcinoma	1	NA, female	Titulaer et al. [5]
Uterine adenocarcinoma	1	71, female	Herein
	1	NA, female	Hara et al. [22]
Mature cystic teratoma of the fallopian tube	1	35, female	Hattori et al. [23]
Testicular tumor	2	30, male; one NA	Titulaer et al. [5]
Thymic carcinoma	1	NA	Titulaer et al. [5]
Metastatic melanoma (brain)	1	50, female	Williams et al. [24]
Gastric cancer	1	55, male	Ding et al. [25]
Pancreatic cancer	1	NA	Titulaer et al. [5]
Colorectal cancer	1	55, NA	Lim et al. [6]
Prostatic cancer	1	64, male	Herein
Sex-cord stromal tumor	1	55, NA	Dalmau et al. [4]
Neuroendocrine tumor	1	55	Dalmau et al. [4]
	1 hepatic neuroendocrine carcinoma	65, male	Lim and Yip [26]
	1 metastatic cells with unknown primary origin	NA	Coban et al. [19]
	1 pancreatic neuroendocrine	50, female	Herein
Hodgkin lymphoma	1	55, NA	Zandi et al. [27]
	2	20, 25, 2 males	Herein
Total	30 (including 8 reported herein)		

NA not available

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Author contributions Dr Chloé Bost: analysis, interpretation of the data, drafting the manuscript for intellectual content. Dr Eve Chanson: analysis, interpretation of the data, drafting the manuscript for intellectual content. Ms Géraldine Picard: acquisition and analysis of data. Dr David Meyronet: acquisition and analysis of data. Ms Marie-Eve Mayeur: acquisition and analysis of data. Dr François Ducray: acquisition of data, critical revision of the manuscript for important intellectual content. Dr Véronique Rogemond: acquisition and analysis of data. Dr Dimitri Psimaras: acquisition of data, critical revision of the manuscript for important intellectual content. Pr Jean-Christophe Antoine: acquisition of data, critical revision of the manuscript for important intellectual content. Pr Jean-Yves Delattre: critical revision of the manuscript for important intellectual content. Dr Virginie Desestret: analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Pr Jérôme Honnorat: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision.

Compliance with ethical standards

Conflicts of interest This study is not industry-sponsored. Dr Chloé Bost reports no disclosures; Dr Eve Chanson reports no disclosures; Ms Géraldine Picard reports no disclosures; Dr David Meyronet reports no disclosures; Ms Marie-Eve Mayeur reports no disclosures; Dr François Ducray reports no disclosures; Dr Véronique Rogemond reports no disclosures; Dr Dimitri Psimaras and Pr Jean-Christophe Antoine report no disclosures; Pr Jean-Yves Delattre reports no disclosures; Dr Virginie Desestret reports no disclosures; Pr Jérôme Honnorat reports no disclosures.

Ethical standards Written consent was obtained from all patients, and this study was approved by the institutional review board of the University Claude Bernard Lyon 1 and Hospices Civils de Lyon.

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