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A rare association of a high grade glioblastoma, cerebral abscess and acute lymphoblastic leukemia in a child with Noonan syndrome

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ABSTRACT

Noonan syndrome is a genetic disorder frequently caused by PTPN11 mutations. Patients with Noonan syndrome are characterized by facial dysmorphism, short stature and congenital heart defects and they have a reported predisposition to malignancies such as leukemia, and solid and central nervous system tumors. Here, we report a case of a 14-year-old boy with Noonan syndrome treated for T-cell acute lymphoblastic leukemia who presented with 2 concomitant abnormalities: cerebral abscess and high grade glioblastoma. This exceptional association exhibits to a poorer prognosis and may sometimes delay the diagnosis and therefore the therapeutic intervention.

Abbreviations list

NS	Noonan syndrome
PTPN11	Tyrosine-protein phosphatase non-receptor type 11
CNS	Central nervous system
HGG	High grade glioblastoma
ALL	Acute lymphoblastic leukemia
CT	Computed tomography
MRI	Magnetic resonance imaging

1. Introduction

Noonan syndrome (NS) belongs to a clinically distinct group of medical genetic syndromes known as RASopathies which are genetic disorders causing dysregulation and hyperactivation in the Ras-mitogen activated protein kinase signaling mechanism [1,2]. NS is known to be a dominant autosomal condition caused by several genetic mutations mainly tyrosine-protein phosphatase non-receptor type 11 (PTPN11) mutations on chromosome 12 [1]. It is characterized by poly-malformative syndrome including facial dysmorphism, developmental delay, congenital cardiac defects and malignancy predisposition [1].

The relationship between patients with NS and childhood malignancies, such as solid tumors, hematologic and central nervous system (CNS) diseases, has been described in the literature [1,3,4].

We report here a case of a patient with NS in whom complications of leukemia treatment revealed the presence of a high grade glioblastoma (HGG).

2. Case presentation

Here, we present a case of a boy, born of a non-consanguineous marriage, who was diagnosed with PTPN11-related NS at the age of six. He was transferred to our hematological department at the age of 14, in October 2019, for T-cell acute lymphoblastic leukemia (ALL). No CNS involvement was noted. Conventional karyotyping showed no chromosomal abnormalities with no hyperdiploidy neither hypodiploidy. The fluorescence in situ hybridization showed no evidence of chromosomal deletions of chromosome 1 nor the t(4;11)(q21;q23). Molecular analysis confirmed the absence of the MLL/AF4 transcript.

The patient was included in the average risk "2" arm of the 58,951 European Organization for Research and Treatment of Cancer-Children's Leukemia Group protocol [5].

Pre-therapeutic echocardiography showed pulmonary artery stenosis and aortic dilatation consistent with the diagnosis of NS with normal left ventricular ejection fraction at 65 %. Thus, we decided to treat him according to the AR1 arm to minimize the risk of cardiotoxicity related to chemotherapy. He received dexamethasone (3 mg/m^2 every 12 h) day1 to day 36. Chemotherapy started at day 8 of the induction course:

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Daunorubicine (30 mg/m^2) and Vincristine (1,5 mg/m^2) on day 8,15,22 and 29 and 8 doses of L'Asparaginase (10.000 UI/m^2). On day 31 of the induction course, he developed continuous fever and worsening headaches. The patient was neutropenic (Neutrophil count at 300 cells/mm^3) and the C-reactive protein was 90 mg/dl. He received empirical intravenous antibiotics. One day after, he developed a tonic-clonic seizure with a moderately impaired mental state. Neurological examination showed left hemiparesis with right hemianopsia. He was not in respiratory distress and his blood pressure was normal. Cerebral computed tomography (CT) showed multiple intracranial ring enhancing lesions of the right hemisphere (Fig. 1).

Prompt magnetic resonance imaging (MRI) with gadolinium contrast demonstrated a 4 cm ring enhancing mass in the right temporal lobe with central necrosis. A second similar 2 cm lesion was located in the right frontal lobe. Diffusion weighted image showed marked hyperintensity and restricted diffusion centrally within both lesions consistent with multiple intracranial pyogenic abscesses. Subsequently, the patient was started on parenteral antimicrobials along with antiepileptics.

Since there was no neurological improvement with persistent fever after five days of continuous intravenous antibiotics, we decided to puncture the frontal abscess. Aspiration of frontal brain abscess was performed under general anesthesia and over 30 mL of greenish purulent fluid was removed.

We observed improvement of the left hemiparesis and headaches subsided within few days. A second brain MRI, performed 2 weeks later, showed a slight regression of the lesions and improvement of the perilesional edema. Aspirated pus showed no growth in bacteriological exams. The white blood count got back to normal (neutrophil count at 2100 cells/ mm^3) with a slight regression of the CRP value (45 mg/dl). Bone marrow assessment after the induction course showed no blasts infiltration.

The patient remained stable for one week, and then he developed transient left upper eyelid myoclonus and spasm of the left hemiface. A Cranial CT scan showed a relapse of the frontal abscess. A repeated puncture and a biopsy of the peripheral capsule were performed.

Histopathologic examination revealed a WHO grade IV glioblastoma (Fig. 2). Given the high-grade malignancy and the multifocal lesions, the decision was to abstain from surgery and to indicate radiotherapy followed by chemotherapy.

The evolution was abruptly marked by the recurrence of holocranial headaches, several focal seizures and persistent fever despite antibiotic therapy and anticonvulsant therapy. Given the altered state of consciousness, radiotherapy was postponed and the patient died four days after glioblastoma diagnosis.

3. Discussion

Children with RASopathies are at an increased risk for hematological and solid malignancies. Several case series have been published in the literature focusing on the occurrence of childhood cancer with an eight

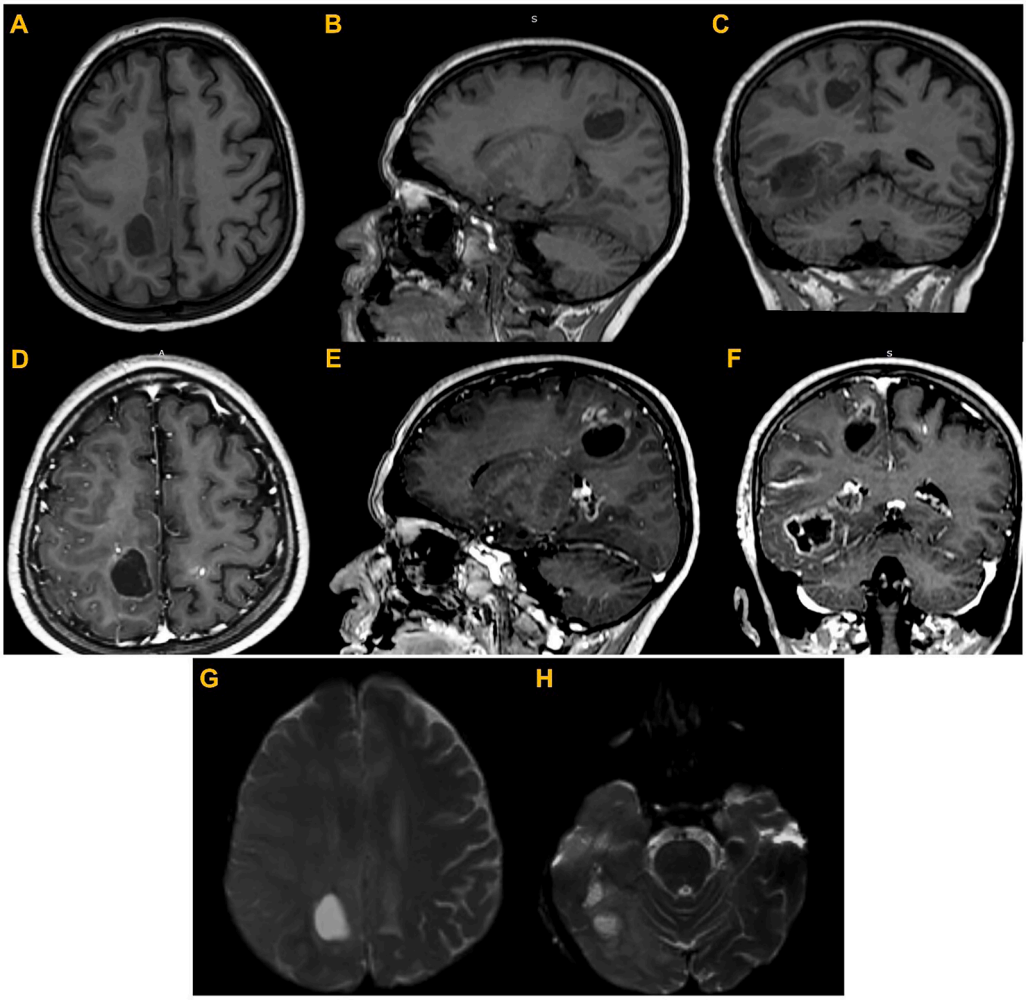

Fig. 1. MRI of the brain. Axial, sagittal and coronal T1-weighted images (A, B &C) show a right parasagittal frontal and temporal lesions with central hypointensity. Postcontrast T1-weighted images (C,D & E) show a thin ring enhancement. On diffusion-weighted images (G & H), lesions demonstrated hyperintensity and central restricted diffusion consistent with an abscess cavity.

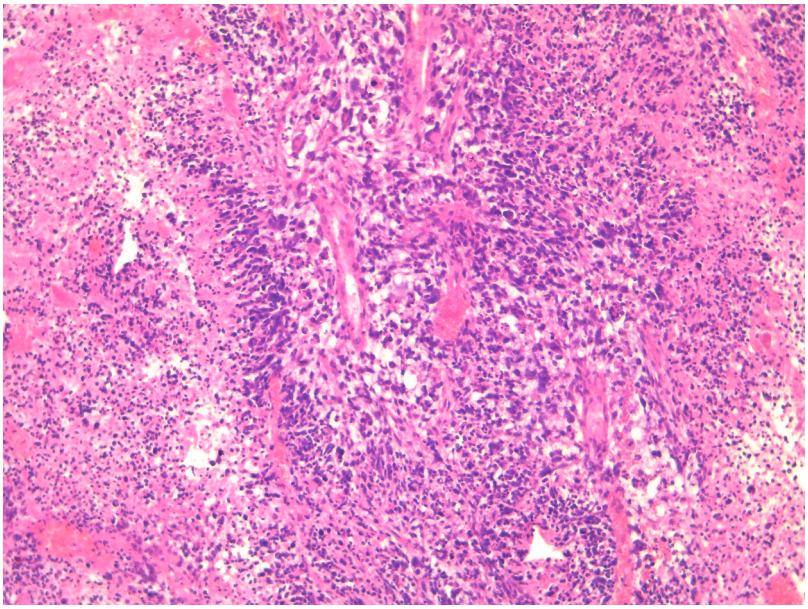

Fig. 2. Histological examination of a cerebral lesion revealed WHO grade IV glioblastoma (Hematoxylin eosin *100).

times increased risk to develop such diseases in NS patients [4]. Furthermore, up to 30 % of cancers in the general population are associated with RAS mutations [2].

Mutation in PTPN11, reported in 25 % of patients, is the most frequent of a myriad of mutations that have been associated with NS [6]. In fact, the PTPN11 gene encodes for a tyrosine phosphatase called SHP2 which controls cell growth through the regulation of RAS-MAPK chain [1]. In NS, the PTPN11 mutation generates a hyperactivated SHP2 that increases phosphatase activity and stimulates cell proliferation and senescence [7]. This PTPN11 mutation has been described to be associated with childhood haematological malignancies including leukaemia [3,8].

Moreover, PTPN11 mutation has been observed with different solid tumors such as liver and lung cancers, melanoma, thyroid carcinoma and brain tumors [9,10]. According to the literature, CNS malignancies in patients with NS are known to be of low grade and are most likely to develop in children rather than in adults [1]. In addition, Kratz et al. described a cumulative incidence of cancers, in NS patients, reaching 4 % by the age of 20 [11].

Although high -grade CNS tumors are rare in patients with NS, El Ayadi et al. described two cases of high - grade (HG) gliomas, which were both anaplastic astrocytomas, proving the occurrence of HGG in NS patients [4,8]. Recently, Khan et al. published the first case of spinal cord glioblastoma multiform in a NS child, which is the third case of HG CNS tumor described in the literature [8]. We present here one more case of a HG CNS malignancy in a NS child who is concomitantly treated for ALL.

The clinical susceptibility to infections in the context of RASopathies has been analysed in a cohort study published in 2021 showing no evidence that these patients are predisposed to develop immunodeficiency and therefore be at a higher risk of serious or unusual infections [12]. In our case, the child developed cerebral abscess during induction chemotherapy agranulocytosis, which may explain the occurrence of this infectious complication in our situation. Otherwise, brain abscess is relatively an uncommon complication in ALL and in case they occur they are generally of fungal nature [13,14].

Brain abscess is generally a secondary process [15]. In most cases, it is associated with a direct bacterial occupation from a contiguous infection (oropharynx, sinus or ear). The haematogenous expand from distinct sources of infection is less common [15]. In our case, the child had febrile neutropenia and was treated with empirical antibiotic therapy with no evidence of local infection or septicaemia. In case of brain tumor, Kalita et al. described that the blood-brain barrier is altered which promotes microbial spread and over-growth [16]. This may explain the occurrence of brain infection in such cases and for our child.

Our patient was diagnosed with glioblastoma after treatment of his brain abscess. According to the literature, the mechanism of such situation may be explained by two phenomena: the development of a brain abscess concomitantly with glioblastoma or de novo glioblastoma (after brain trauma) [17]. In the second situation, for some authors, a period of at least one year between the brain injury and the development of the tumor must be required [17]. According to this criterion and given the progressive growth of brain tumors, our case fulfils more the criterion of the development of a brain abscess within a pre-existent glioblastoma.

The triad of a cerebral abscess, HGG and ALL is exceptional in NS patients. The prognosis is extremely bad in such situation. Oriented surveillance is mandatory in this context given the predisposition to hematological malignancies and the heterogeneity of clinical signs.

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Consent to participate

The authors declare that an informed and a written consent was obtained from the parents of the patient prior to the publication of the case and the accompanying images.

CRediT authorship contribution statement

Wiem Boufrikha: Data curation, Writing – original draft. **Rim Rakez:** Writing – review & editing. **Inaam Bizid:** Data curation, Supervision, Writing – original draft. **M.Maher Hadhri:** Data curation, Writing – review & editing. **Manel Njima:** Data curation, Supervision, Validation. **Sarra Boukhris:** Supervision, Validation. **M.Adnene Laatiri:** Supervision, Validation.

Declaration of Competing Interest

The authors declare no conflicts of interest in relation with this

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