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Juvenile Systemic Lupus Erythematosus and Glioblastoma: A Case Report and Literature Review

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Abstract. This is a case report of 11-years-old Chadian female, diagnosed with juvenile systemic lupus erythematosus based on five out of eleven criteria of the American College of Rheumatology. Her disease was under control on oral prednisolone, azathioprine and hydroxychloroquine. One year after diagnosis, she presented to the emergency department complaining of severe headache, vomiting and deterioration in the level of consciousness. Urgent brain computed tomography scan showed large brain tumour in the left parietooccipital region with significant midline shifting. Craniotomy and excisional biopsy of the mass was performed by a neurosurgeon. Histopathology reports a high grade malignant glioblastoma multiforme. Three cases were reported in the literature as space occupying lesion in the brain in juvenile systemic lupus erythematosus. To our knowledge, glioblastoma multiforme is the first case to report in juvenile systemic lupus erythematosus. Thus, severe headache and unusual neurological manifestations in juvenile systemic lupus erythematosus may be related to space occupying lesion, and should be evaluated immediately for early medical and surgical management.

Keywords: Systemic lupus erythematous, Glioblastoma, Brain tumor.

Case Report

An 11 years old Chadian girl presented to Emergency Department of King Abdulaziz University Hospital, complaining of fever for 2 months, weight loss and fatigability. She was completely healthy till two month

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prior to admission, she presented with daily fever, cough and weight loss. The fever was relieved by antipyretic for few hours, and associated with chills, but no sweating. The cough was reproductive with small amount of the sputum white in colour (does not contain blood) she has been seen by many physicians in polyclinic and received few courses of antibiotics without any improvement. She lost weight around 10 kilogram, with decreased appetite and activity. There was history of skin rash on the face when she was exposed to sunlight. There was no history of arthralgia, headache, urinary symptoms, history of travel, and contact with patients with tuberculosis (TB). No history of eating of raw meat or fish, and of animal exposure. She received her regular vaccinations.

Systemic review was unremarkable. There is no family history of rheumatic disease and infections such as TB. She lives in very poor district of Jeddah with very low income.

Examination at initial admission showed pallor, no jaundice or cyanosis, clubbing, edema, and there was generalized lymphadenopathy. She was febrile, other vital signs and growth parameters were normal. She had non-inflamed hypertrophied tonsil and no mouth ulcers. Chest, abdomen, and CNS examination was normal. Musculoskeletal examination showed no arthritis and/or myositis. She was admitted in to the hospital as a case of fever of unknown origin for investigation.

Initial laboratory tests showed: Normal white blood count (WBC) 6.25 K/uL (4.5-13.5) with mainly lymphocytosis 28.4% (10-15), neutrophils 64.5% (35-65), monocyte 2.6% (2-11), and normochromic normocytic anemia with hemoglobin (Hb) 9.1 g/L, and normal platelets count 371 K/uL (150-400). Peripheral blood film showed no malaria and blood smear was negative for blast cell. Erythrocyte sedimentation rate (ESR) was 150 mm/hr, and C-reactive protein (CRP) was 44.1. Blood, urine and sputum cultures were negatives, and urine analysis was unremarkable. Brucella antibody titre and workup for TB was negative. Viral serology for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reported positive immunoglobulin M (IgM); however, blood cultures for viruses were negative. Lymph node biopsy revealed reactive lymph node, and bone marrow examination reported no malignancy.

She was seen by Pediatric rheumatologist 3 weeks after admission who detected vasculitic ulcers on the hard palate. The results of following immunological investigations revealed positive antinuclear

antibody (ANA) titre > 1:1280, speckled pattern, and anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA) 665 IU/ml (0-200). Anti-Smith antibody and direct Coombs test were positive. Complement level was normal. Patient diagnosed systemic lupus erythematosus (SLE) based on 5 out of 11 (Photosensitivity rash, oral ulcers, Coombs positive hemolytic anemia, positive ANA, anti-dsDNA) classification criteria of the American College of Rheumatology (ACR) for SLE[1].

Patient was treated with intravenous methylprednisolone pulse therapy daily for 3 days and maintenance therapy on azathioprine 50 mg orally daily, hydroxychloroquine 200 mg OD, prednisolone 15 mg PO BID and omeprazole 20 mg daily. Patient discharged home in good condition with appointment to outpatient clinic.

Patient showed good compliance to medication. In her last visit to the clinic, she was stable and disease was in remission. One year later from the diagnosis she developed on and off severe headache mainly in frontal region, all over the day, no reliving or aggregative factor associated with vomiting. The headache becomes worse, day after day with multiple emergency department visits. In each time, she was given acetaminophen and sent home by emergency room physician. One month later she presented to emergency room with severe headache, frequent vomiting and neurological abnormalities with disorientation and decreased in the level of consciousness.

She was irritable with GCS 13/15, Temp 36.8°C, HR 50-60, RR: 30, BP 77/65 and oxygen saturation 100% in room air.

Central nervous system examination (CNS) examination showed pupils equally reactive bilaterally, left side hemiplegic, increased tone and reflex in left upper and lower limb. Normal tone, power and reflexes in right upper and lower limb; right upper motor neuron facial palsy. Other examination was unremarkable. Patient underwent urgent brain computed tomography (CT) scan (Fig. 1) and admitted to paediatric intensive care unit.

Patient treated with brain edema measurement, and an urgent neurosurgery consultation was performed.

Craniotomy and excisional biopsy showed high grade malignant glioma with feature mixed glioma (Grade IV astrcoytoma - glioblastoma multiforme) (Fig. 2).

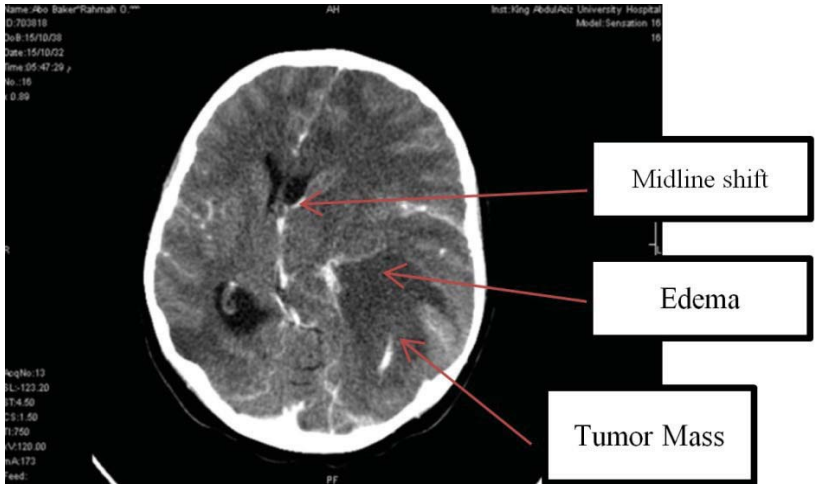

Fig. 1. **CT brain showed left parietooccipital large intraparenchymal space – occupying lesion with significant midline shift.**

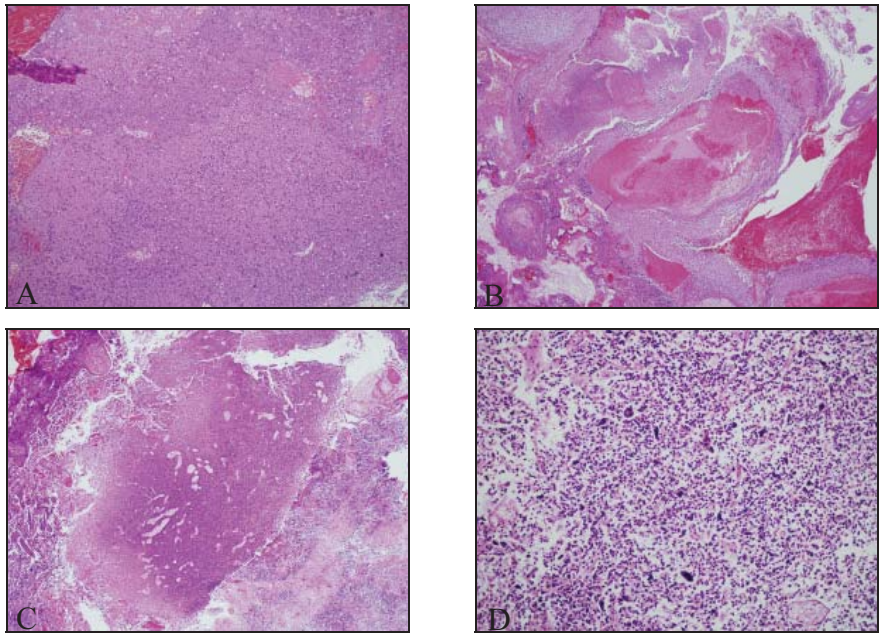

Fig. 2. **Hisopathology of brain tumor: A. Microvascular proliferation; B. Area of necrosis and hemorrhage; C. Area of necrosis surrounding; D. Neoplastic cell, high cellularity, nuclear pleomorphism, hyperchromasia and infrequent mitosis, frequent giant cells by neoplastic cell.**

Since the brain tumor was large and highly malignant mass, surgical intervention was not possible. Therefore, the patient was treated with 14 radiotherapy session, and haematology started her in glioma protocol[2] in addition to supportive measurement of brain oedema and analgesic. Patient did not respond to the treatment and died 10 months later.

Discussion

Glioblastoma multiforme (GBM) is a high malignant brain tumor that usually occurs in adult with peak incidence between 45 and 70 years[3], and only occasionally encountered in pediatric age group[4]. Lymphoproliferative disorders has been reported frequently in SLE, as an associated complication in adult[5] and rarely in paediatrics. However, brain tumor in association with SLE has not been reported in adult. The prevalence of nervous system involvements in SLE is reported between 22 – 95% in children. The clinical manifestations widely variable, ranging from severe, life-threatening symptoms at presentation, such as transverse myelitis, to symptoms of more subtle and subclinical abnormalities of neurocognitive function[6]. These manifestations are mainly related to active CNS lupus with nonspecific radiological changes. Unusual neurological manifestation secondary to brain lesion were reported in three children with SLE[7-9].

In these reports, headache, unusual neurological manifestation and other systemic symptoms were the leading cause of presentation to the clinic and diagnosing the brain lesion. Our patient was presented with significant headache and later with disorientation, right facial palsy and left hemiplegia.

The first case was reported in a 13-year-old Caucasian female. She was diagnosed with SLE based on the presence of arthritis, antinuclear antibodies, and double-stranded DNA, and pleural effusion. She was investigated for amenorrhea, and galactorrhea. Her serum prolactin level was significantly elevated. The diagnosis of pituitary prolactinoma was made on the radiological and histological finding of the brain lesion. Improvement in the menstruation and in clinical manifestation with decreased prolactin levels, and reduced levels of inflammatory markers was observed after surgical resection of the tumor and treatment with bromocriptine mesylate[7].

The second case presented with sudden onset of change of consciousness. Urgent brain Magnetic resonance imaging (MRI) showed a huge cerebral tumor in a 14 years old girl with SLE lupus nephritis who was under regular steroid therapy. Histology reported as cerebral perivasculitis. Neurological symptoms improved after surgical decompression and corticosteroid pulse therapy[8].

Third case reported presented with right hemiparesis and headache for 10 days duration in a 19 years old adult female, with SLE and Moyamoya disease diagnosed before 16 year of age. Brain MRI showed large tumour in left frontoparietal lobe with necrotic area, histopathological examination of the lesion reported neuroectodermal tumour. Outcome of this patient and detail management was not reported in the abstract[9].

Our case with mixed glioblastoma had not been reported in children or in adult in association with SLE in most of the literatures and text books. The exact etiology of both the GBM and SLE is unknown. Our patient was treated with azathioprine and hydroxychloroquine for SLE, and treated with corticosteroid, hydroxychloroquine and azathioprine.

In the literature, the medication used in our patient as possible cause of brain tumour was reviewed. Azathioprine was found to be a safe drug and does not cause malignancy in SLE. However, it may increase risk of lymphoma in patients with inflammatory bowel disease[10]. Chloroquine reported as safe and effective drug in lupus patients. When added to convectional treatment of GBM in a randomized double-blind, placebo-control trial chloroquine found to improve mid-term survival[11]. Thus, we could not hypothesize the exact etiology of brain tumour in SLE patients. In spite of appropriate conventional therapy and continuation of hydroxychloroquine our patient did not survive.

Conclusion

Brain tumor is a rare complication in juvenile SLE and GBM, and has not been reported before. Severe headache and unusual neurological manifestations in children with SLE should be evaluated radiologically, without delay for brain space occupying lesion for early intervention and treatment.

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التهاب الذئبة الحمراء الحمامية الجهازية وورم الدماغ الأرومي الدبقي في مرحلة الطفولة

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المستخلص. طفلة أفريقية تبلغ من العمر ١١ عاماً تعاني من مرض الذئبة الحمراء وتم تشخصيها منذ عام بناء على خمسة معايير من أحد عشر معيار من الكلية الأمريكية لأمراض الروماتيزم (ACR) وكان المرض تحت السيطرة باستخدام الكورتيزون والأزاثايوبرين والهيدروكسي–كلوروكوين وبعد سنة ذهبت إلى حجرة الطوارئ وهي تشكو من صداع شديد وقيء واختلاف في مستوى الوعي، تم عمل أشعة مقطعية على الدماغ والذي أظهر ورماً في الجهة اليسرى للفص القذالي والجداري أدى إلى انحراف خط الوسط تمت استشارة جراح المخ والأعصاب الذي قام بأخذ عينة بواسطة شق الجمجمة وإرسالها إلى مختبر علم الأمراض، وقد أشار تقرير علم التشريح النسيجي إلى أن الورم دبقي من الدرجة العالية مع ميزة مختلطة. وتظهر هذه الحالة ارتباطاً غير متوقع بين مرض الذئبة الحمراء وورم الدماغ الدبقي الأرومي ولذلك يجب أن يكون الصداع الشديد وورم الدماغ الدبقي من ضمن التشخيص التفريقي للظواهر العصبية عند الأطفال الذين يعانون من مرض الذئبة الحمراءالحمامية الجهازية.