Case Reports

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p.48 Fulminant Purpuric Rash in a Toddler

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A Review of Rare Extra-Nodal Non-Hodgkin’s Lymphoma

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Non-Hodgkin’s Lymphoma (NHL) constitutes 5% of all cancers worldwide. Of these, 10–35% are extra-nodal in origin. Renal involvement in lymphoma occurs in 30–60% of cases as per a 2008 report.\(^1\) Primary renal lymphoma is a rare entity defined as NHL arising from renal parenchyma, not resulting from invasion of an adjacent lymphomatous mass.\(^2,3\) Common presenting symptoms include flank pain, renal insufficiency, hematuria, fever, and weight loss.\(^4\) In the absence of chemotherapy, it can disseminate rapidly from the primary site and 75% of patients die within a year.\(^5\)

CASE DESCRIPTION

A 35-year-old man with a significant history of diabetes mellitus 2 and hypertension presented with a 30 pound weight loss in the last 6 months, bilateral facial weakness with dysphagia, dysarthria, and gradually increasing intermittent bilateral flank pain for one month. He had an episode of hematuria four months prior to this hospitalization.

On examination, right lumbar tenderness was present. Neurologically, he had cerebellar nystagmus, opsoclonus, facial diplegia, bilateral facial numbness, palatal weakness and truncal ataxia. Abdominal CT showed a 14x10 cm right renal mass. (Figure 1) MRI brain showed T2 flair hyperintensities involving genu, inter-body and splenium of corpus callosum, periventricular deep white matter surrounding lateral ventricles, optic tract, hypothalamus, superior cerebellar peduncle, right cerebral peduncle, bilateral middle and inferior cerebellar peduncles, and upper medulla. (Figures 2,3) The CT of the chest did not show evidence of any primary or metastatic tumor. Infectious disease workup for HIV, hepatitis B, Lyme titer, HSV 1 and HSV 2, VDRL and mycoplasma antibody were negative. Cerebrospinal fluid analysis showed lymphocytic pleocytosis, high protein with normal glucose, negative cryptococcal and lyme antigens and negative anti-Ro, Hu, YO and Ma2 antibodies. Based on the MRI findings and clinical presentation, a diagnosis of paraneoplastic brainstem encephalitis was made.
Pathology of the resected right kidney showed features of a large lymphocytic infiltration. (Figure 4) Subsequent immunohistochemistry was positive for CD 20, CD 10, and BCL-6 consistent with diffuse large B-Cell lymphoma. (Figures 5, 6, 7) Patient was started on Rituxan, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy. Despite chemotherapy, a repeat MRI brain showed progressive bilateral medial temporal lobe involvement interpreted as limbic encephalitis. Due to worsening mental status, the patient was transferred to the intensive care unit where he passed away due to respiratory failure.

**DISCUSSION**

Extra-nodal presentation of NHL occurs in 25–35% of cases, and the most common sites involved are stomach, skin, small intestine, breast, thyroid, lung, heart, liver, genitourinary tract, adrenals and bones. Primary renal lymphoma is a rare type of extra-nodal NHL constituting 0.7% of all extra-nodal lymphomas. It is very aggressive and associated with high mortality. There are three criteria for diagnosing primary renal lymphoma: (1) lymphomatous renal infiltration, (2) non-obstructive uni- or bilateral kidney enlargement, and (3) absence of extra-nodal localization at time of diagnosis. Using the above criteria, of all the 60 cases originally reported, only 28 cases met the diagnostic criteria. Histopathologically, renal lymphoma usually of small cells (Burkitt’s) or large B-cell type and will be positive for CD 20 and CD 10 upon immune-histochemical examination.

Cases of primary renal lymphoma with paraneoplastic brainstem and limbic encephalitis have been reported. Brainstem encephalitis is characterized by nystagmus, opsoclonus, cranial nerve paresis, dysarthria, dysphagia and central autonomic dysfunction. Limbic encephalitis is characterized by a subacute onset of short-term memory loss, seizures, confusion, and symptoms of hypothalamic dysfunction. MRI of the brain will show unilateral or bilateral medial temporal abnormalities in limbic encephalitis. Our patient was a unique example of both, as he initially presented with nystagmus, opsoclonus, and facial diplegia, and during his hospital course progressed to altered mental status and confusion.
CSF analysis in paraneoplastic syndrome will show an inflammatory picture in 80% of cases with mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), increased protein levels and variable presence of oligoclonal bands (due to intrathecal synthesis of IgG). These types of paraneoplastic neurologic syndromes are associated with presence of Anti Hu, Ma2, Yo, Ro antibodies. The presence of anti-neuronal antibodies in serum or CSF may help in making diagnosis but they are positive in only 60% of cases. Therefore it is important to exclude other differential diagnoses that can mimic the same neurological picture. In our case, CT of the whole body was performed and found to be negative for any other primary or metastatic disease. Infectious workup for HIV, hepatitis, fungal serology, Lyme serology was negative and CSF examination for infectious etiology was also negative. The ACE level was checked to rule out sarcoidosis (low sensitivity, high specificity) and was negative. The diagnosis of paraneoplastic encephalitis was made due to lack of evidence for other causes including other malignancies (especially small cell lung cancer, breast cancer, etc.). The cause of paraneoplastic syndrome with primary renal lymphoma has not been well established yet. Encephalitis associated with such paraneoplastic syndrome responds poorly to treatment, and the role of plasmapheresis, IVIG and immunosuppressive therapy has not been established.

CONCLUSION

There is no solid evidence that can establish the predisposition for development of primary renal lymphoma. Reported cases have been increasing since 2000. Paraneoplastic syndromes have been reported to be associated with primary renal lymphoma. Despite chemotherapy, this tumor is very aggressive and there is a need for further research into treatment options.

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REFERENCES


Fulminant Purpuric Rash in a Toddler
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A previously healthy 15-month-old male born at 36-week gestation presented to an outside emergency department with a 1-day history of low grade fever, nasal congestion, cough, and worsening maculopapular erythematous rash. He was reported to have normal developmental milestones and up to date immunization except his first MMR vaccine. Patient did not attend day care and there was no recent history of travel or sick contacts in the family. His temperature was 104°F, heart rate was 200 beats/minute, and blood pressure was not measurable.

CASE REPORT
Within the next few hours, the rash became generalized and progressed to purpuric lesions. An intravenous line was accessed and crystalloid fluid was administered, along with intravenous ceftriaxone, vancomycin, and dexamethasone. He was then airlifted to our facility’s intensive care unit. Initial physical assessment was significant for a toxic-appearing child with a temperature of 103.1°F, heart rate of 220 beats/minute, and respirations of 60 breaths/minute; neither blood pressure nor pulse oximetry could be detected. There were generalized purpuric lesions in his entire body, with predominance over the face, torso, and lower extremities. (Figure 1) He was cyanotic with poor peripheral perfusion and impalpable distal pulses. He was emergently intubated and placed on mechanical ventilation, along with central venous and arterial catheters. Central venous pressure was measured to be 3 cm H2O. Complete blood count was significant for leukocytosis 22250 cells/mm3 with 20% bands, decreased hemoglobin 10.2 gm/dL, decreased hematocrit 29.7%, and thrombocytopenia 34,000 platelets/mm3. Complete metabolic panel was significant for hyponatremia 128 mmol sodium/L, azotemia with BUN 27 mg/dL, and elevated AST 99 IU/L. Coagulation profile revealed the presence of disseminated intravascular coagulation, with significantly elevated INR 3.7, and prolonged PTT 89.8 seconds, depleted fibrinogen 64 mg/dL, in addition to his thrombocytopenia. Arterial blood gas analysis revealed compensated metabolic acidosis, with pH 7.35, pCO2 20 mmHg, HCO3 11 mmol/L, and base deficit 12 mmol/L. He was stabilized initially with copious volume expansions, and dopamine, nitroprusside and milrinone infusions to achieve adequate blood pressure. His condition was too labile to attempt lumbar puncture, but latex agglutination studies from the referring hospital detected Neisseria meningitidis antigens of serogroups C and/or W-135 in serum and urine. He was given a ten day course of intravenous ceftriaxone, and high-risk contacts received oral rifampin prophylaxis.

The patient’s hospital course was complicated by several factors. His anemia and thrombocytopenia initially worsened, with hemoglobin decreasing to 7.5 g/dL on hospital day two, and platelets decreasing to 8000 platelets/μL on day four. This was treated with multiple infusions of packed red blood cells, fresh frozen plasma, and platelets. His liver enzymes also initially continued to increase, peaking on day three with AST 2780 IU/L and ALT 2087 IU/L, before trending towards normal, which suggested ischemic liver injury. Additionally the patient’s ears and lower legs became increasingly cold, hard, and discolored, and creatine kinase was found to be massively elevated at 145,900 IU/L. Later his areas of purpuric skin began forming small blisters that eventually progressed to large, tense bullae. (Figure 2) Despite precautions, the bullae began to slough off, leaving significant areas of denuded skin. He was transferred to the regional intensive care burn unit where he eventually required bilateral amputations below the knee and reconstructive surgery for
the external ears. At last follow-up he was reported to be active and playing catch with burn unit staff. Long-term neurological outcome remains unknown.

DISCUSSION

Along with inflammation of the meninges, invasive meningococcal infection can result in fulminant septic shock, and less commonly, pneumonia, pericarditis, or septic arthritis. The incidence of invasive meningococcal infection in the US is approximately 0.5–1.1 cases per 100,000 people, with the highest incidence among children under age five. Among children, the highest incidence occurs in children <1 year old at 9.2 cases per 100,000. Neisseria meningitidis, the causative agent of invasive meningococcal disease, is an encapsulated Gram-negative diplococcal bacteria carried by asymptomatic colonizers in the upper respiratory tract. It is transmitted via respiratory secretions. The incubation period is on average four days ranging from two to ten days. While epidemics can occur, over 95% of cases are sporadic.

There are at least 13 strains, or serogroups, of N. meningitidis, with classification based on chemically-distinct capsular polysaccharides. Serogroups A, B, C, Y, and W-135 are most commonly implicated in invasive disease, though the proportion of cases caused by each specific serogroup varies by location and host age group. In the US, serogroups B, C, and Y each account for approximately 30% of cases, while A and W-135 are more frequently associated with cases in the Middle East and Africa. Among infants, more than 50% of cases are caused by serogroup B, for which there is currently no available vaccine. Besides close living conditions, children with immunodeficiencies, such as late component complement deficiency or anatomic or functional asplenia, are at increased risk for invasive disease due to limitations in host immunity.

CLINICAL PRESENTATION AND MANAGEMENT

Onset of invasive meningococcal infection can be abrupt, and it can progress very rapidly from onset of fever to death in as little as 12 hours. Early symptoms are typically nonspecific “flu-like” complaints, such as fever, chills, malaise, headache, nausea, and rash. The classic petechial rash of meningococcemia can develop subtly prior to any change in mental status, and may initially appear as a nonspecific macular or maculopapular rash. However, signs of meningeal irritation are not necessarily always present. A patient with fever and non-blanching petechial rash should strongly be considered to have invasive meningococcal disease until proven otherwise and appropriate testing and treatment must be initiated without delay.

When meningococcal infection is suspected, blood and CSF cultures should be collected, though lumbar puncture could be deferred in circumstances in
which subjects rapidly progressing to DIC or hemodynamically compromised. Organisms may be detected in cultures of skin lesions, synovial fluid, and sputum in some patients; however, detection of N. meningitidis in nasopharyngeal samples should not be considered diagnostic, as approximately 10% of the population carry the bacteria asymptomatically.² Polymerase chain reaction testing can be used to detect specific serogroups. A positive CSF bacterial antigen detection test in a symptomatic patient suggests a probable case even without culture confirmation. Serum or urine latex agglutination assays of the polysaccharide antigen are considered less compelling, and are not recommended for diagnosis.³

Regardless of obtaining samples or test results, treatment—with intravenous penicillin G, cefotaxime, ceftriaxone or ampicillin, or chloramphenicol in patients with penicillin allergy—should be started immediately upon suspicion of meningococcal infection. Droplet precautions should be maintained for at least 24 hours after initiation of antibiotics. Supportive measures and rapid transfer of the patient to a tertiary care center, preferably a facility with pediatric ICU capabilities, is recommended. Patients transferred to tertiary centers with antibiotics initiated at the referral source have better outcomes than those sent without their first dose of antibiotic. Volume resuscitation requirements are often extensive, and early intubation and ventilation should be considered to optimize oxygenation in the poorly perfused patient. Despite rapid treatment, some patients may still deteriorate rapidly and require supportive care for shock. Waterhouse-Friderichsen syndrome, multi-system organ dysfunction, ischemic extremities, disseminated intravascular coagulation, and coma.³ Early diagnosis, appropriate antibiotic therapy, and supportive measures have contributed to a significant reduction in overall case-fatality rates, which have decreased from 50–10%.² However, about 10–20% of survivors have significant permanent neurological sequelae or limb loss.¹

POST-EXPOSURE PROPHYLAXIS
Antibiotic prophylaxis is indicated for high-risk contacts of individuals with meningococcal disease, as the attack rate for household contacts is 500–800 times higher than the rate in the general population.³ High-risk contacts include those having close contact with the infected individual over the 7 days prior to the onset of disease, and up to 24 hours after initiation of antibiotics. Ideally, all high-risk contacts should receive antibiotic prophylaxis either with rifampin (5–10 mg/kg/dose x 4 doses), or alternatively, single dose of ceftriaxone or ciprofloxacin¹ within 24 hours of diagnosis of the index case. Prophylaxis is considered unnecessary if contact occurred more than 14 days earlier, as the incubation period for invasive disease is usually 4 days and no greater than 10 days.⁴ Antibiotic is not recommended for low-risk contacts, and mass chemoprophylaxis is not encouraged to control outbreaks, due to the cost, drug side effects, and emergence of resistant organisms.

VACCINATION GUIDELINES
There are currently two vaccines available against N. meningitidis in the US, both of which provide protection against serogroups A, C, Y and W-135 but not serogroup B: meningococcal polysaccharide vaccine (MPSV4 or Menomune⁶, Sanofi Pasteur Inc, Swiftwater, PA), and meningococcal conjugate vaccine (MCV4 or Menactra⁷, Sanofi Pasteur Inc, Swiftwater, PA). The Advisory Committee on Immunization Practices recommends routine vaccination of 11–18 year olds with MCV4 at the earliest opportunity, preferably during the routine preadolescent visit at age 11. MCV4 vaccine should be offered to all unvaccinated college freshmen living in dormitories, and to military recruits. MCV4 is also recommended for children age two to ten years old with risk factors for invasive meningococcal disease.⁸

VACCINATION FOR CHILDREN YOUNGER THAN TWO YEARS
Currently, there are no vaccines licensed in the US for children younger than two years of age, as both MPSV4 and MCV4 are poorly immunogenic in this population. However, there is an investigational quadrivalent vaccine, MenACWY-CRM197 (Menveo⁷, Novartis Vaccines and Diagnostics, Cambridge, MA), now under phase III clinical trial which has shown high levels of immunogenicity in infants two months of age and older, with comparable safety and efficacy to MCV4.⁹

CONCLUSION
Because of initial vague symptoms, rapid progression, high mortality rates, and devastating sequelae, it is critical that healthcare providers recognize this dis-
ease in its early stage, initiate antibiotic therapy and supportive care, and seriously consider referral to tertiary healthcare facilities in no time if necessary.

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REFERENCES


2. Centers for Disease Control and Prevention, Meningococcal disease, in CDC Health Information for International Travel 2010: Yellow Book. 2009, U.S. Department of Health and Human Services, Public Health Service: Atlanta, GA.


