

中文題目：隱球菌腦膜炎引起之腦脊髓液單株免疫球蛋白反應

英文題目：Isolated cerebrospinal fluid monoclonal gammopathy in a case of Cryptococcus meningoencephalitis

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Introduction

Humoral immunity plays an important role in our immune system. Beyond innate immunity, there is much diversity and specificity of adaptive humoral immunity which help us to fight against numerous pathogen. During the development of maturation, B cell experiences affinity enhancement, class switching and differentiation of plasma cell and memory B cell. Through all the process mentioned above, the B cell is able to produce functional immunoglobulin, called antibody, to amplify our innate immunity and protect us from illness. [B lymphocytes: how they develop and function, PMID:18725575] However, there would be some diseased process during the B cell maturation and resulted in abnormal colony expansion. Usually, infection and inflammation responses illicit polyclonal B cell activation and polyclonal immunoglobulin produced as consequence. By contrast, abnormal clonal expansion and monoclonal gammopathy developed in B cell lymphoproliferative disease including multiple myeloma and some specific type of lymphocytic leukemia and lymphoma. Here, we present a case challenging this concept with manifestation of monoclonal gammopathy in infectious disease.

Case report

This is a 49-year-old female with underlying disease of hypertension. She worked as a logistic picker and denied any specific pets or chemical substance exposure history. She had suffered from severe headache for 2 weeks with character as intermittent, unilateral but alternating in lateralization each time, over temporal-frontal area, combined with nausea, vomiting, photophobia and phonophobia. She had taken over-the-counter medication for pain control and visited local clinic for several times but in vain. On 2019/2/18, she visited out emergency room for progressive and intractable headache. Brain computed tomography(CT) was performed and no remarkable structural lesion detected. Lumbar puncture with cerebrospinal fluid(CSF) analysis was processed as evaluation of secondary headache under inform-consent. CSF study revealed high opening pressure 298mmH₂O, pleocytosis 222/microliter, elevated CSF protein level and positive India ink stain. Followed culture report had yielded Cryptococcus neoformans. Specific contact history was reviewed again and the patient claimed that there were some pigeon wondering in the park nearby her house and possible contact with their dropping accidentally. Induction therapy with amphotericin B plus flucytosine was delivered as management and followed by maintenance fluconazole. Surprisingly, IgG λ monoclonal band had been found on the immunofixation electrophoresis(IFE) of CSF specimen as a routine test in our hospital. However, negative IFE result in serum and urine specimen detected. Repeated CSF IFE showed reproducibly positive result and CSF

immunoglobulin quantification revealing significant elevated IgG(18.7mg/dl, reference level < 3.4mg/dl). There was no obvious clinical symptoms associated to multiple myeloma or lymphoma observed. Bone marrow study was also conducted and no dysplasia involved. Brain Magnetic Resonance Imaging (MRI) was conducted and revealing enhancing lesions with mixed high signal intensity on T2WI over bilateral cerebellar hemispheres, bilateral basal ganglia, right frontal, parietal and temporal lobes with largest one at the right pre-central gyrus 1.8 centimeter. Cryptococcoma was impressed but the patient refused surgical biopsy as exclusion of possible malignancy. Under antibiotic treatment, clinical manifestation was improving and series CSF study disclosing decreasing monoclonal band reaction on CSF IFE. This patient was then under regularly follow up at clinic and free of neurologic deficit.

Discussion

In 1890, an serum agent which can neutralize diphtheria toxin was found by von Behring and Kitasato and the name “antibody” created. In 1939, serum was separated into albumin, alpha-globulin, beta-globulin, and gamma-globulin fractions by Tiselius and Kabat via electrophoresis method. Besides, gamma-globulin area was consumed by serum-antigen mixture reaction and defined as the main population of antibody. The basic composite of immunoglobulin include heavy chain and light chain. Functionally, they could be separated into antigen-binding variable domains and Fc receptor-binding domains. Five class of heavy chain with IgM, IgG, IgA, IgD, and IgE isotypes was defined, also 2 class of light chain with κ and λ isotope documented. [Structure and Function of Immunoglobulins PMID: 20176268]. After contact with antigen, mature B cell would undergo class switch process in response to antigen stimulation and co-stimulation factor.[Mechanism and Regulation of Class Switch Recombination, PMID: 18370922]

In normal host response, due to diversity of antigenic property on pathogen, different lineage of B cells are involved even in one single evading pathogen and polyclonal immunoglobulin produced as defense mechanism. In contrast, abnormal B cell proliferation disorder, such as multiple myeloma, lymphoblastic leukemia or lymphoma, may present with monoclonal immunoglobulin production due to uncontrolled single lineage B cell proliferation.

In our case, interesting finding with isolated CSF monoclonal gammopathy is found and no other evidence of systemic lymphoproliferative disease documented. Repeated CSF study confirms the indeed existence of CSF monoclonal gammopathy, also quantitative analysis reveals high level of IgG. Though, CSF light chain quantification cannot be performed due to laboratory facility limitation. Bone marrow biopsy dose not reveal significant abnormality. CSF flowcytometry is not available due to scanty cell amount in CSF specimen. Brain MRI discloses multiple enhancing lesion with unknown nature. Cryptococcoma is favored clinically but malignancy still cannot be ruled out. Surgical biopsy had been suggested but refused by the patient. Followed CSF study

showed fading monoclonal band on IFE under anti-Cryptococcal therapy which compatible to clinical improvement.

In our hypothesis, the isolated CSF monoclonal gammopathy may be triggered by *Cryptococcus meningoenzephalitis* infection, which challenges our basic knowledge about B cell immune reaction and activation in response to pathogen. In literature review, there is another case report of a 41-year-old woman with candida fungemia presenting as serum monoclonal gammopathy. [Transient monoclonal gammopathy induced by *Candida* fungemia, PMID:29180248] It seems that there is possibility of monoclonal immunoglobulin expansion triggered by specific pathogen but how and why this happened need more investigation. Besides, the importance to follow up and risk of indolent B cell proliferative disease should still be kept in mind. Great improvement in knowledge of adaptive immunity would be made once we figure out the exact mechanism of our hypothesis and a whole new landscape would be seen.