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Tumefactive Demyelinating Lesions and Pregnancy

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Abstract

Until now, only one gestational tumefactive demyelinating lesion (TDL) has been described. Here we report two TDL cases occurring during and after the pregnancy. A 26-year-old 6-week pregnant woman developed a 3-cm left frontotemporoparietal subcortical TDL with inhomogeneous partial enhancement. Brain biopsy revealed a subacute demyelinating lesion with abundant macrophages and mild chronic perivascular inflammatory infiltrates. She also had femoralpopliteal deep vein thrombosis. During the 4-year follow-up, magnetic resonance imaging showed only residual biopsied TDL. The second case was a 41-year-woman affected by both multiple sclerosis (MS) and rheumatoid arthritis who developed a 2-cm right anterior corona radiata TDL with sporadic gadolinium-enhancing "annular spots" eight months after delivery. After steroid therapy at the 6-month radiological follow-up, this TDL was half-reduced. Five years earlier, at the beginning of her MS, she already had a 2-cm TDL with incomplete ring enhancement. These two described TDLs formed in prothrombotic conditions and were likely representative of thromboinflammation around and inside the small-medium veins.

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Full Text

Tumefactive demyelinating lesions (TDLs), or lesions greater than 2 cm with "tumor-like" characteristics, were recently the subject of several case reports and reviews.[1],[2],[3],[4] The biggest challenge in the diagnosis of TDL is represented by their early differentiation from brain tumors since a response to steroid therapy, suggestive radiological imaging or even indicative histopathological examination can allow for certain diagnosis.[4] During pregnancy, the difficulty of diagnosis increases due to the restricted use of diagnostic tests potentially harmful to both mother and child health. However, one case of gestational TDL has been previously described in the literature.[5] We reported two cases occurring either during an early pregnancy and 8 months after delivery.

Case History

Case report 1

On January 25, 2014, a 26-year-old previously healthy 6-week pregnant woman was admitted to the hospital for an acute right sensory-motor syndrome. Electrocardiogram, echocardiogram, epiaortic ultrasound, thrombophilia tests (coagulation factors, complement, homocysteine, protein S, activated protein C resistance, antithrombin-III), autoantibodies (ANA, anti-ENA, ANCA, anticardiolipin, LAC), blood cytometry, and thyroid function were unremarkable except for reduced protein S (42%, 60–160). Viral serology including HIV was also negative. Brain magnetic resonance imaging (MRI) showed a 3-cm left frontotemporoparietal subcortical lesion with no mass effect or edema. A central vein was visible within the lesion and the values of the apparent diffusion coefficient (ADC) were reduced with a slightly increased peripheral diffusion [Figure 1]a and [Figure 1]b. Intravenous methylprednisolone 1 gram once daily for five days was administered without clinical improvement. After five days, a contrast-enhanced MRI scan confirmed the same-size lesion with both inhomogeneous partial enhancement and three to four times increased cerebral blood volume compared with contralateral values [Figure 1]c. MRI spectroscopy showed increased choline and reduced N-acetylaspartate peaks. A lumbar puncture revealed increased protein (61 mg/dL, 15–45) and positive oligoclonal bands. On February 10, enoxaparin 6000 UI twice daily was started for a right occluding femoral-popliteal deep vein thrombosis (DVT). A brain biopsy was performed on February 27, after voluntary termination of pregnancy and caval filter placement. Histological examination showed abundant macrophages (CD68+), myelin loss with preservation of axons, reactive gliosis, and mild chronic perivascular inflammatory infiltrates, highly suggestive for a subacute demyelinating lesion. The patient continued enoxaparin 4000 IU once daily for 6 months with complete DVT resolution. Repeated controls of thrombophilia tests yielded normal results including protein S. During the 4-year follow-up, brain and spinal cord MRI showed only residual biopsied TDL with no new demyelinating lesions [Figure 1]d while only mild sensory-motor syndrome persisted.{Figure 1}

Case report 2

On April 5, 2017, eight months after delivery, a 41-year-old woman affected by multiple sclerosis (MS) since October 2012 and by rheumatoid arthritis (RA) since April 2013 presented a subacute remarkable left hemiparesis with impaired walking. On admission, brain MRI showed a 2-cm right anterior corona radiata lesion with mass effect and sporadic gadolinium-enhancing "annular spots" [Figure 2]a. Intravenous methylprednisolone (1 g/day) for 7 days was administered followed by oral prednisone 50 mg/day for 15 days with gradual clinical improvement. At clinical and radiological 6-month follow-up, only a mild left arm weakness persisted, whereas a 2-cm right corona radiata lesion reduced to 12-mm length with both significant reduction in mass effect and gadolinium-enhancement disappearance [Figure 2]b. Five years earlier, at the onset of her MS in October 2012, the patient already had a large TDL in the corpus callosum left corona radiata region with incomplete ring enhancement [Figure 2]c. At that time, all blood tests including Borrelia burgdorferi and autoantibodies (anti-ANA, anti-ENA, pANCA, cANCA, anti-phospholipid) were normal, while

oligoclonal bands were positive. In April 2013, she manifested signs of RA confirmed by the positivity for both rheumatoid factor and anti-citrullinated protein antibodies (141 U/mL, normal value <20 U/mL). She was treated with copaxone 20 mg subcutaneous and prednisone 25 mg/day per os from November 2013 to January 2016 when she suspended the therapy due to pregnancy. On August 3, 2016, she gave birth to a healthy baby and decided not to resume therapy to breastfeed. In May 2017, copaxone 40 mg subcutaneous (1 fl × 3/week) was re-started.{Figure 2}

Discussion

To best of our knowledge, only one gestational TDL case has been previously described in the literature.[5] Similarly, MS exacerbations are uncommon in the course of pregnancy, especially in the third trimester, in contrast to cerebral ischemic and venous thrombotic complications of childbearing. These events are likely due to either the prothrombotic pregnant condition or the increased production of estrogens. Furthermore, due to endocrine-modulating feedback, childbearing determines a state of immune tolerance that permits the growth of the semi-allogeneic fetus expressing paternally derived antigens.[6] This immune condition is mainly mediated by adaptive immunity both suppressing cell-mediated and enhancing antibody-mediated protection that lead to the placental and systemic shift from Th1 toward Th2 dominance. Indeed, predominantly cell-mediated diseases such as MS and RA improve, whereas predominantly antibody-mediated disorders such as systemic lupus erythematosis and antiphospholipid syndrome usually worsen during pregnancy. It is important to highlight that coagulation is part of innate immunity and has considerable proinflammatory and immune-modulatory effects so much so that new concepts such as thromboinflammation and immunothrombosis, connecting inflammation and thrombosis through the activation of innate immunity, were recently introduced.[7] Thus, a procoagulant state in pregnancy represents not only a hemostatic challenge of placenta delivery but also an increased innate immune response, probably needful to compensate a reduced cell-mediated immunity.

In our first case, DVT and reduced protein S level in the absence of genetic coagulopathy likely reflect a pregnant hypercoagulable state albeit unusually premature for the patient's 6-week gestation period. In the second patient, the disease exacerbation could be expected because both MS and RA usually activate after delivery; however, the TDL formation is singular. Interestingly, this patient developed a TDL also at her disease onset, regardless of pregnancy. Because the pathogenetic mechanisms of RA occur on the vasculitis basis,[8] a TDL formation in this case is likely a consequence of venous inflammatory thrombotic events. In fact, the presence of a central vein is clearly visible in both our cases [Figure 1] and [Figure 2]. Furthermore, the central vein sign represents a pathognomonic characteristic of both TDLs and MS lesions.[9],[10] The vasocentricity of TDLs helps distinguish them from the glioma because TDL forms around a vein, whereas a glioma invades, displaces, and encloses vascular structures.[9] Indeed, there is some overlapping not only on conventional MRI but also on MR spectroscopy, diffusion and perfusion MRI, and even on histopathologic examination of stereotactic biopsy.[3],[9] Typical pathological findings of TDLs include hypercellular lesions with confluent demyelination, abundant foamy macrophages containing myelin debris, reactive astrogliosis, relative axonal preservation, and variable perivascular and parenchymal lymphocytic inflammation.[11] However, about 30% of small biopsies may be misdiagnosed especially with low-grade astrocytoma due to the presence of astrocytic pleomorphism, variable nuclear atypia, a rare mitotic figure, and occasional necrosis or cystic changes.[11] In addition, TDLs have several clinical characteristics of small-medium venous thrombosis.[12]

We previously hypothesized that an impaired cell-mediated response to noxa patogena in the brain might be at the basis of TDL pathogenesis during MS-modifying therapies or other pathologies.[13] In fact, the formation of TDLs happens more frequently during fingolimod treatment, which typically reduces circulating

lymphocytes. The dysfunction of T-lymphocytes could lead to the persistence of the noxa patogena's action determining lesion progression. A new pathogenic concept of immunothrombosis supports a continuum of thromboinflammation at the level of the cerebral venous system manifesting as prevalently inflammatory around the venules in MS lesions, thromboinflammatory inside and around small-medium veins in TDLs, and widely thrombotic in cerebral sinovenous thrombosis. This trend during pregnancy could be explained by the unbalancing of thromboinflammation toward its prothrombotic innate immune component leading to a higher incidence of cerebral vascular lesions compared with that of inflammatory lesions.

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Conflicts of interest

There are no conflicts of interest.

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