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EFFECTS OF MATERNAL CYTOMEGALOVIRUS INFECTION ON FETAL IMMUNE ORGANS DEVELOPMENT. CLINICAL CASE

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Abstract

Introduction: Cytomegalovirus (CMV), a ubiquitous herpesvirus, causes congenital infection in 0.5–2% of live births, leading to severe manifestations like hepatosplenomegaly, microcephaly, and neurological damage. CMV evades immunity by manipulating apoptosis via Bcl-2 upregulation and p53 suppression, disrupting thymic and splenic development critical for T-cell education and peripheral immunity. This case report examines morphological changes and expression of apoptosis (Bcl-2, p53) and proliferation (Ki-67) markers in fetal thymus and spleen from a 23-week miscarriage due to maternal CMV infection.

Materials and Methods: Autopsy of fetus from a 28-year-old woman's fourth pregnancy (late miscarriage at 23 weeks) provided thymus and spleen samples. Macroscopic and microscopic assessments followed standardized algorithms. Immunohistochemistry used monoclonal antibodies (Bcl-2 Clone 124, p53 Clone DO-7, Ki-67 Clone MIB-1; DAKO) with LSAB2®-HRP and diaminobenzidine chromogen. Results were quantified via Histo score (McCarthy et al., 1985).

Results: Thymus showed enlargement, large lobules (cortex:medulla 2:1), preserved lymphocytes, and moderate Hassall's corpuscles. Spleen exhibited splenomegaly, white:red pulp 1:2, activated white pulp, and marginal zone clusters. Bcl-2 stained cytoplasmically in thymic medulla and splenic marginal zone; p53 was weakly positive in thymic cortex/medulla; Ki-67 was pronounced in thymic subcapsular cortex and splenic periarteriolar lymphoid sheaths.

Discussion: Thymic hyperplasia and preserved lymphocytes indicate CMV-driven proliferation over atrophy, with Bcl-2 medullary dominance suggesting impaired negative selection and autoreactive T-cell survival. Splenic white pulp expansion reflects immune activation, but disorganization and Bcl-2/Ki-67 upregulation imply exhaustion and dysregulation. A decrease in p53 levels may indicate a disruption of the apoptotic process.

Conclusion: CMV profoundly alters fetal thymus/spleen morphology and apoptosis/proliferation, disrupting T-cell repertoire and self-tolerance, contributing to long-term immunological sequelae.

Key Words: *CMV-infection, fetal thymus, spleen, Bcl-2, p53, Ki-67, apoptosis*

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Резюме

ВЛИЯНИЕ МАТЕРИНСКОЙ ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИИ НА РАЗВИТИЕ ИММУННЫХ ОРГАНОВ ПЛОДА. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Введение: Цитомегаловирус (ЦМВ), повсеместно распространенный герпесвирус, вызывает врожденную инфекцию у 0,5–2% новорожденных, приводя к тяжелым проявлениям, таким как гепатоспленомегалия, микроцефалия и неврологические повреждения. ЦМВ избегает иммунитета, манипулируя апоптозом посредством повышения уровня Bcl-2 и подавления p53, нарушая развитие тимуса и селезенки, критически важных для обучения Т-клеток и периферического иммунитета. В данном клиническом случае рассматриваются морфологические изменения и экспрессия маркеров апоптоза (Bcl-2, p53) и пролиферации (Ki-67) в тимусе и селезенке плода после выкидыша на 23-й неделе беременности, вызванного материнской ЦМВ-инфекцией.

Материалы и методы: Образцы тимуса и селезенки плода от четвертой беременности (поздний выкидыш на 23-й неделе) 28-летней женщины. Макроскопическая и микроскопическая оценка проводилась в соответствии со стандартизированными алгоритмами. Для иммуногистохимического исследования использовались моноклональные антитела (Bcl-2, клон 124, p53, клон DO-7, Ki-67, клон MIB-1; DAKO) с LSAB2®-HRP и окраской диаминобензидиновым хромогеном. Результаты количественно оценивались с помощью гисто-счета (McCarthy et al., 1985).

Результаты: Тимус показал увеличение линейных размеров, большие дольки (соотношение кора:мозговое вещество 2:1), сохраненное количество лимфоцитов и умеренное количество телец Гассалля. Селезенка показала

спленомегалию, соотношение белой и красной пульпы 1:2, активированную белую пульпу и скопления клеток в краевой зоне. Bcl-2 окрашивался цитоплазматически в мозговом веществе тимуса и краевой зоне селезенки; p53 был слабоположительным в коре/мозговом веществе тимуса; Ki-67 был выражен в субкапсулярной коре тимуса и периартериальных лимфоидных оболочках селезенки.

Обсуждение: Гиперплазия тимуса и нормальное количество лимфоцитов указывают на пролиферацию, вызванную ЦМВ, а не на атрофию, при этом доминирование Bcl-2 в мозговом веществе предполагает нарушение негативной селекции и выживаемости аутореактивных Т-клеток. Увеличение белой пульпы селезенки отражает активацию иммунной системы, но дезорганизация и повышение уровня Bcl-2/Ki-67 указывают на истощение и дисрегуляцию. Снижение уровня p53 может свидетельствовать о нарушении процесса апоптоза.

Заключение: ЦМВ существенно изменяет морфологию фетального тимуса/селезенки и апоптоз/пролиферацию, нарушая репертуар Т-клеток и аутотолерантность, способствуя развитию долгосрочных иммунологических последствий.

Ключевые слова: *ЦМВ-инфекция, фетальный тимус, селезенка, Bcl-2, p53, Ki-67, апоптоз*

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Түйіндеме

АНАЛЫҚ ЦИТОМЕГАЛОВИРУС ИНФЕКЦИЯСЫНЫҢ ҰРЫҚТЫҢ ИММУНДЫҚ МҮШЕЛЕРІНІҢ ДАМУЫНА ӘСЕРІ. КЛИНИКАЛЫҚ ЖАҒДАЙ

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Кіріспе: Цитомегаловирус (CMV), кең таралған герпесвирус, жаңа туған нәрестелердің 0,5–2%-ында туа біткен инфекцияны тудырады, бұл гепатоспленомегалия, микроцефалия және неврологиялық зақымдану сияқты ауыр көріністерге әкеледі. CMV Bcl-2 деңгейінің жоғарылауы және p53 басылуы арқылы апоптозды манипуляциялау арқылы иммундық жүйеден жалтарады, бұл Т жасушаларының жиналуы және перифериялық иммунитет үшін маңызды болып табылатын тимус пен көкбауырдың дамуын бұзады. Бұл клиникалық жағдай туралы есепте ананың CMV инфекциясынан туындаған жүктіліктің 23 аптасында түсік тастағаннан кейін ұрықтың тимус пен көкбауырындағы морфологиялық өзгерістер мен апоптоздық (Bcl-2, p53) және пролиферация (Ki-67) маркерлерінің экспрессиясы зерттеледі.

Материалдар мен әдістер: 28 жастағы әйелдің төртінші жүктілік кезіндегі (23 аптада кеш түсік тастаған) ұрықтың тимус және көкбауыр үлгілері пайдаланылды. Макроскопиялық және микроскопиялық бағалау стандартталған алгоритмдерге сәйкес жүргізілді. Иммуногистохимия үшін LSAB2®-HRP және диаминобензидин хромоген бояуы бар моноклоналды антиденелер (Bcl-2 клоны 124, p53 клоны DO-7, Ki-67 клоны MIB-1; DAKO) пайдаланылды. Нәтижелер гисто-балл арқылы сандық анықталды (McCarthy және т.б., 1985).

Нәтижелер: Тимус сызықтық өлшемдерінің ұлғаюын, үлкен бөлікшелердің (қыртыс:ми безінің қатынасы 2:1), лимфоциттер санының сақталуын және орташа Гассалл денешелерінің болуын көрсетті. Көкбауырда спленомегалия, ақ/қызыл пульпа қатынасы 1:2, белсендірілген ақ пульпа және шеткі аймақта жасушалық агрегаттар байқалды. Bcl-2 тимус ми безі мен көкбауырдың шеткі аймағында цитоплазмалық боялған; p53 тимус қыртысында/ми безінде әлсіз оң нәтиже көрсетті; Ki-67 субкапсулярлы тимус қыртысында және көкбауырдың периартериалды лимфоидты қабықтарында экспрессияланды.

Талқылау: Тимус гиперплазиясы және лимфоциттердің қалыпты саны атрофия емес, CMV тудырған пролиферацияны көрсетеді, ал милы затында Bcl-2 басым болуы аутореактивті Т- жасушаларының теріс іріктеуі мен тіршілік етуінің бұзылуын көрсетеді. Көкбауырдың ақ пульпасының ұлғайуы иммундық белсенділікті көрсетеді, бірақ ұйымдаспағандық және Bcl-2/Ki-67 деңгейінің жоғарылауы сарқылу мен реттелудің бұзылуын көрсетеді. p53 деңгейінің төмендеуі апоптоз процесінің бұзылуын көрсетуі мүмкін.

Қорытынды: CMV ұрықтың тимус/көкбауыр морфологиясын және апоптоз/пролиферациясын айтарлықтай өзгертеді, Т-жасушаларының репертуарын және өзін-өзі төзімділігін бұзады, ұзақ мерзімді иммунологиялық салдардың дамуына ықпал етеді.

Түйінді сөздер: *CMV инфекциясы, ұрықтың тимусы, көкбауыр, Bcl-2, p53, Ki-67, апоптоз*

Дәйексөз үшін:

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Introduction

Cytomegalovirus (CMV) is the causative agent of one of the most common viral infections in the world, which is usually asymptomatic in immunocompetent individuals. CMV is a DNA herpesvirus belonging to the family Herpesviridae, characterized by its ability to establish lifelong latency despite immune surveillance. Presently, CMV can be encountered in every fourth woman of childbearing age, with seroprevalence rates exceeding 80% in some populations [1, 2]. Cytomegalovirus represents one of the most significant causes of congenital infection globally, affecting approximately 0.5–2% of all live births, making it the leading infectious cause of congenital disease worldwide [3, 4, 5].

Clinical manifestations in infants with symptomatic congenital CMV infection at birth are present in only 5–10% of intrauterinely infected infants, though this represents a significant proportion of symptomatic disease. The clinical spectrum includes hepatosplenomegaly (75%), petechiae (65–80%), growth retardation (70%), jaundice (65%), microcephaly (45–50%), and periventricular calcification of the brain (45%) [6, 7]. Congenital CMV infection can affect virtually every organ system, including the thymus and spleen - primary and secondary lymphoid organs crucial for immune system development and function.

CMV has evolved sophisticated strategies to evade host immune responses and promote survival of infected cells. A fundamental survival strategy involves biphasic regulation of cellular Bcl-2 family proteins - key arbiters of mitochondrially-mediated apoptosis [8]. The immediate-early (IE) and early viral proteins of CMV directly counteract apoptotic pathways: IE2 protein binds to and suppresses the transcriptional functions of p53, a critical tumor suppressor and apoptosis inducer, while other viral proteins (pUL36 and pUL37) directly inhibit procaspase-8 and pro-apoptotic proteins (Bax and Bak), respectively [9, 10].

CMV-infected cells exhibit upregulation of anti-apoptotic Bcl-2 and transient elevation of Mcl-1, followed by sustained Bcl-2 expression, creating a permissive intracellular environment for viral replication [8]. This is accomplished through integrin signaling pathways, wherein viral envelope glycoproteins (particularly the pentameric gH/gL/UL128-131 complex) engage cellular integrins to trigger pro-survival signaling cascades.

The thymus represents a primary lymphoid organ essential for T-lymphocyte development and education. Thymic development begins as early as week 8 of human gestation, with organized cortical and medullary regions by the second trimester. The first T-lymphocytes emigrate from the fetal thymus and populate the periphery by 12–14 weeks of gestation [11]. Humans accomplish most T-cell development in utero, with a dramatic increase in thymic cellularity during the third trimester.

Congenital CMV infection elicits marked immune responses despite the typically underdeveloped neonatal immune system. Infected fetuses generate strong CD8+ T cell responses that can be detected as early as 22 weeks of gestation, with oligoclonal expansions of CMV-specific CD4+ T cells displaying a Th1 phenotype [12, 13]. However, these responses demonstrate functional exhaustion characterized by elevated expression of the inhibitory receptor PD-1, reduced production of IL-2 and other effector cytokines, and high frequencies of terminally differentiated CD57+ CD28– cells [14, 15].

The purpose of this clinical report description is to present morphological changes in fetal thymus and spleen in a case of CMV infection during pregnancy and to study the expression of apoptosis markers: bcl-2, p 53 and the cell proliferation marker ki-67 in the lymphoid component of the thymus and spleen of human fetuses with congenital CMV infection.

Materials and methods

The following is a case report of a 28-year-old woman with clinically and laboratory confirmed cytomegalovirus infection, who was in her fourth pregnancy and experienced a late spontaneous miscarriage at 23 weeks' gestation. Using autopsy material, we assessed the morphological characteristics of the fetal thymus gland and spleen (macroscopic parameters and microscopy). Immunohistochemical studies were performed with primary monoclonal antibodies to bcl-2 (Clone: 124 “DAKO”), p 53 (Clone: DO-7 “DAKO”), and ki-67 (Clone: MIB-1 “DAKO”). For immunostaining of the reaction products, the Kit LSAB2® System-HRP (“DAKO”) visualization system was used with the chromogen diaminobenzidine, which yielded a dark brown stain. Nuclei were counterstained with hematoxylin. The results of the immunohistochemical reaction were assessed using the semiquantitative Histo score method according to *McCarthy et al.* (1985).

Research Results:

Autopsy examination revealed enlarged thymic dimensions measuring 3.2 × 2.7 cm with weight of 3.15 g, exceeding age-appropriate norms for 23-week gestation [16]. This thymic enlargement represents a critical finding, as an infection may potentially leads to a reactive lymphoid hyperplasia or an inflammatory response that disrupts the normal maturation of the fetal immune system. Linear dimensions and weight of the fetal spleen were markedly elevated above age-appropriate norms for 23-week gestation, and compiled 1,7 × 3,3 cm with weight of 2.10 g, that means pronounced enlargement (splenomegaly).

Microscopic Architecture:

Microscopic examination of the thymus was conducted in accordance with and based on the "Algorithm for Assessment of Morphological Features of the Thymus" developed by *Professor Yu.V. Pruglo* (1996). A predominance of large lobules was observed, with a cortex-to-medulla ratio of 2:1. The stroma was poorly defined, congestive hyperemia was observed, and there was no decrease in the lymphocyte count in the cortex or medulla. A moderate number of medium-sized Hassall's stratified corpuscles was observed per lobule. The ratio of white to red pulp of the spleen in the CMV-infected fetus was 1:2, demonstrating a predominance of red pulp but with paradoxical sharp increase and activation of white pulp structures. Numerous small forming lymphoid follicles without clear boundaries between individual nodules were observed, with clusters of cells conspicuously present in the marginal zone - the specialized microenvironment separating white and red pulp compartments.

Immunohistochemical Analysis of Apoptosis and Proliferation Markers

Bcl-2 Expression: Immunohistochemical analysis using monoclonal antibodies against Bcl-2 (Clone 124, DAKO) revealed a positive immunohistochemical reaction manifested by cytoplasmic staining of lymphocytes, predominantly localized to the thymic medulla with fewer immunopositive cells detected in the cortex. Bcl-2 Expression in Splenic White Pulp: a positive immunohistochemical reaction to Bcl-2 was observed with cytoplasm staining of lymphocytes, predominantly localized to the marginal zone. (Fig1, Fig 2).

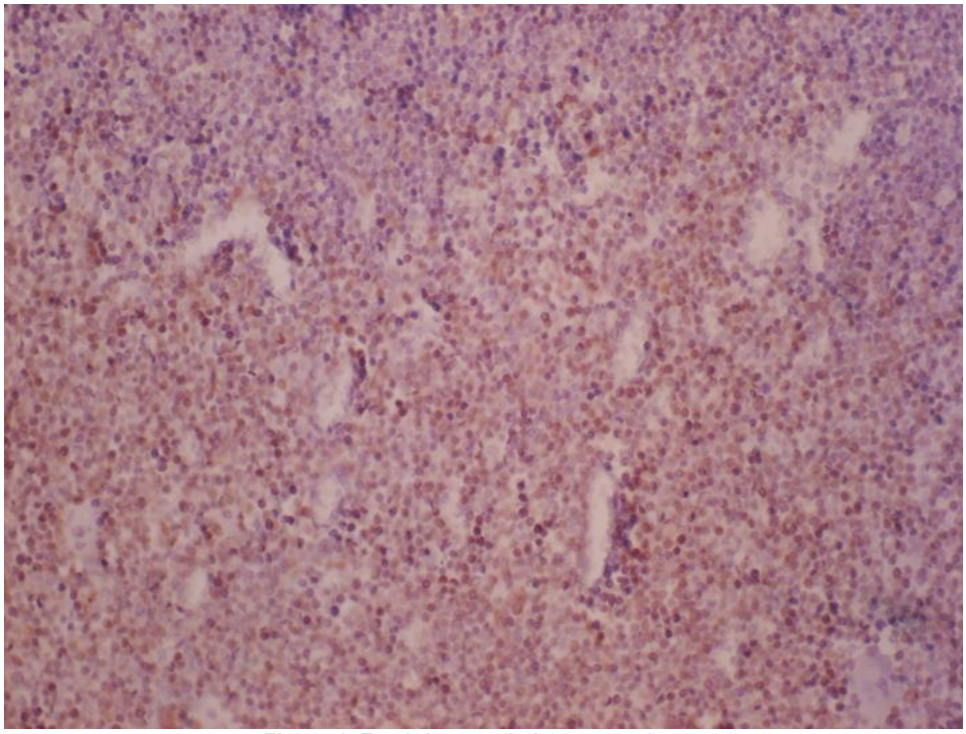

Figure 1. Fetal thymus, bcl-2 expression, x 20.

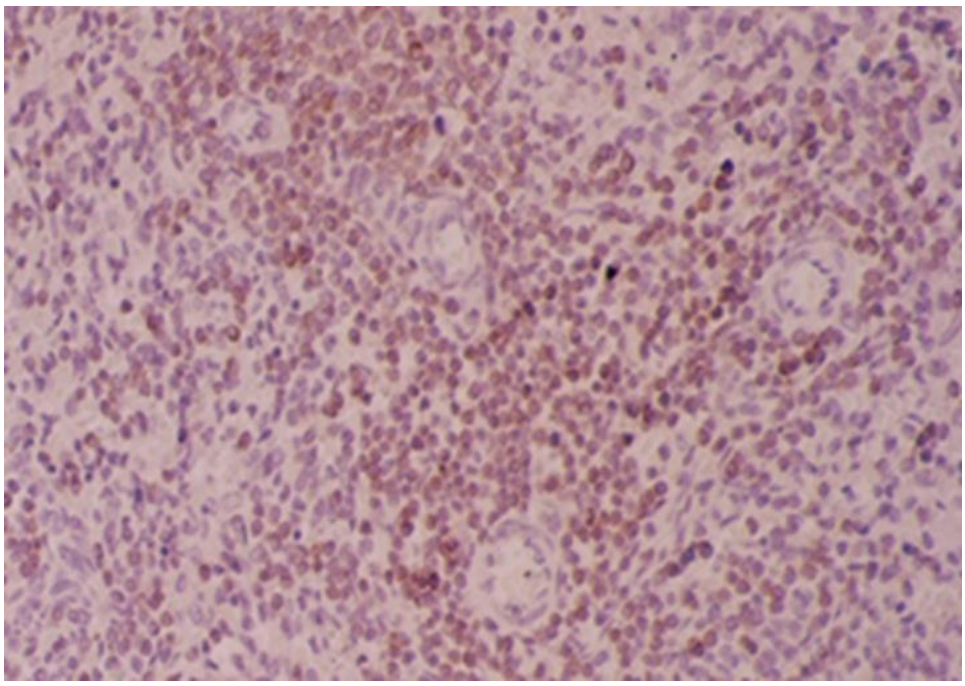

Figure 2. Fetal spleen, bcl-2 expression, x 20.

Ki-67 Expression:

Ki-67 expression was well expressed in lymphocytes in the cortex of the thymus, particularly pronounced in the subcapsular zone where early thymocyte precursors accumulate and proliferate. Ki-67 expression was pronounced in the periarterial lymphoid tissue (PALS) - the T-cell zones surrounding central splenic arteries. (Fig3, Fig 4).

p53 Expression: Expression of p53, the critical tumor suppressor and apoptosis-inducing transcription factor, was weakly positive in both cortical and medullary regions of the thymus (Fig5).

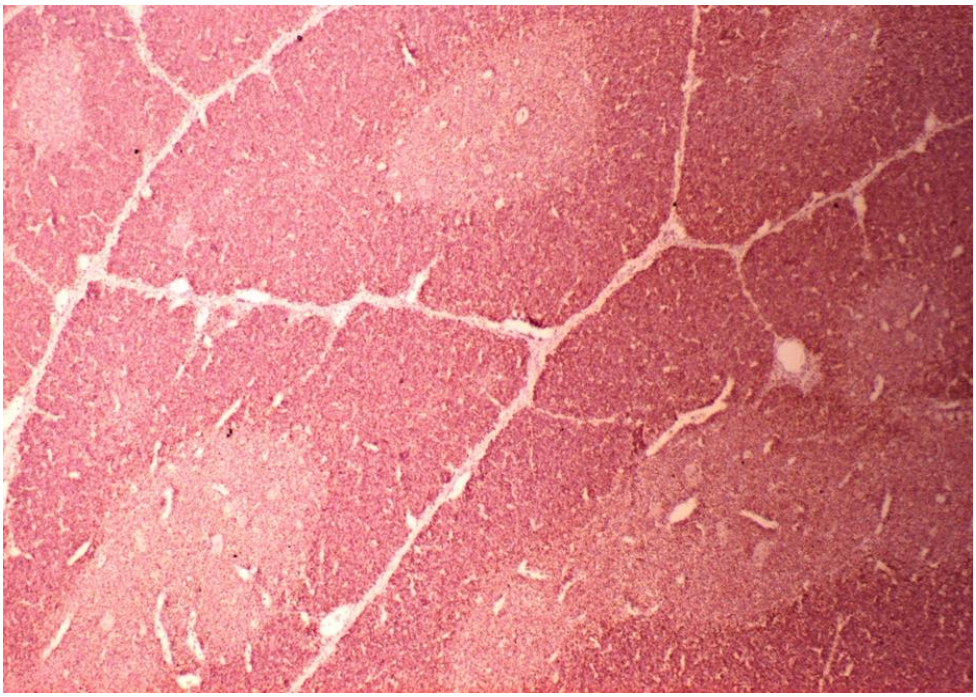

Figure 3. Fetal thymus, ki-67 expression, x 20.

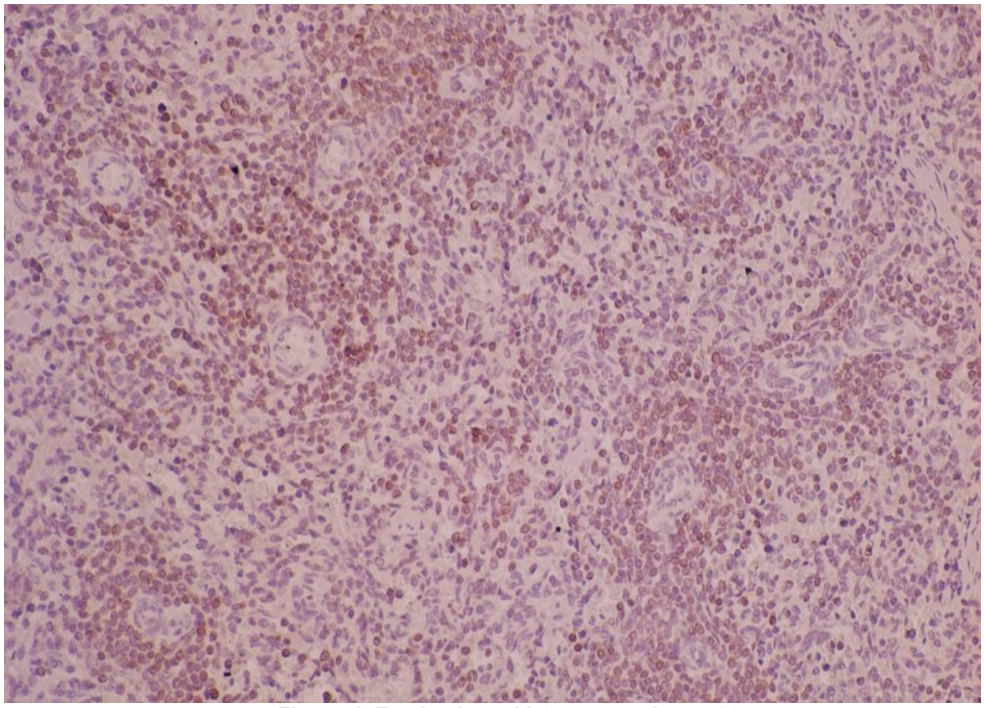

Figure 4. Fetal spleen, ki-67 expression, x 20.

Discussion

The macroscopic enlargement of the thymus in congenital CMV infection likely reflects a paradoxical response to infection: while the thymus normally exhibits involution (shrinkage) during systemic infection in older individuals, the developing fetal thymus may respond to viral infection with hyperplasia as an attempt to generate enhanced immune responses or alternatively due to infection-related disruption of normal developmental signals.

The splenomegaly represents one of the most common clinical signs of symptomatic congenital CMV infection, occurring in 75% of symptomatic neonates at birth.[50] The normal ratio white and res pulp at this gestational age is approximately 1:3, indicating relative expansion of white pulp in this infected specimen despite absolute increase in red pulp mass.

Detailed microscopic examination, conducted according to standardized morphological assessment algorithms, revealed significant architectural alterations compared to normal fetal thymus. This elevated cortex-to-medulla ratio indicates either relative expansion of the cortical (epithelial-rich) compartment or reduction of the medullary compartment.

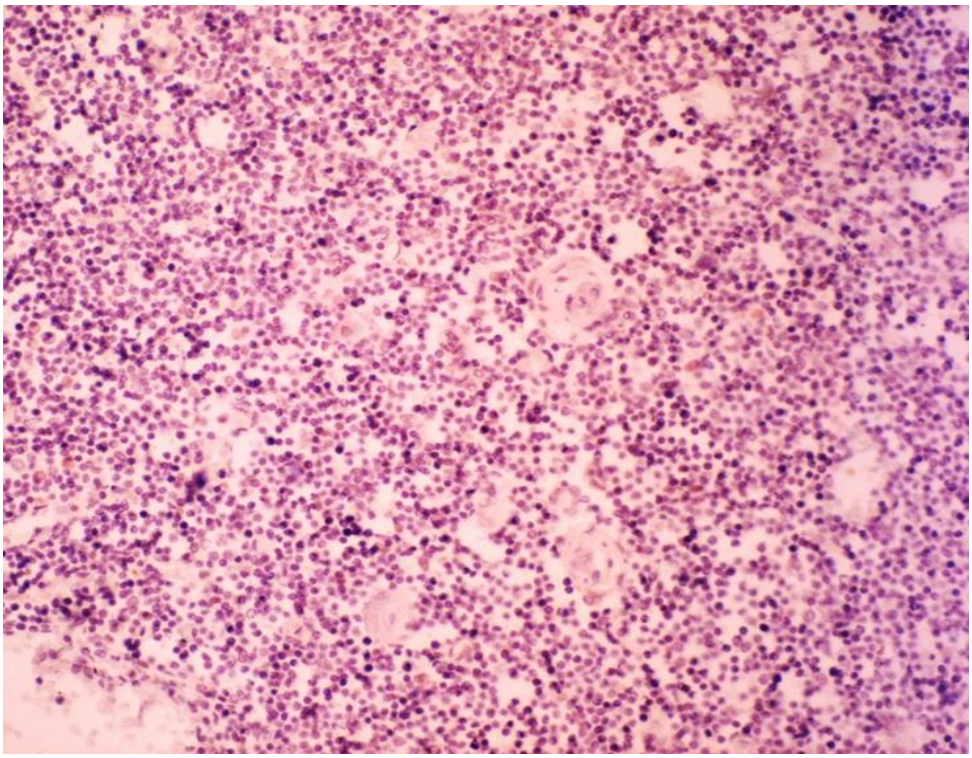

Figure 5. Fetal thymus, p 53 expression, x 20.

Critically, there was no decrease in lymphocyte count in either the cortex or medulla, distinguishing this case from classical viral-induced thymic atrophy characterized by rapid lymphocyte depletion. This preservation of lymphocyte numbers despite architectural distortion suggests that CMV primarily disturbs thymic epithelial organization rather than causing direct cytolytic elimination of thymocytes.

Hassall's corpuscles are aggregates of post-Aire differentiated medullary thymic epithelial cells (post-Aire mTECs), representing terminally differentiated epithelial structures that express thymic stromal lymphopoietin (TSLP) and contribute to the pro-inflammatory thymic microenvironment crucial for central tolerance induction [17]. The presence of intact Hassall's corpuscles, though numerically moderate, is notable, as severe viral infections can induce increased numbers of these structures and disarrangement of thymic epithelium.

The abnormal splenic architecture reflects profound splenic lymphoid hyperplasia in response to CMV infection. The white pulp comprises periarteriolar lymphatic sheaths (PALS) - T-cell zones surrounding central arteries - and lymphoid follicles containing B-lymphocytes [18]. Activation and proliferation of these white pulp structures indicates robust, albeit immature, splenic immune response to viral antigen.

The relative decrease in red pulp area, resulting primarily from a decrease in sinusoid volume, suggests that actively proliferating lymphoid tissue may have mechanically displaced normal erythrocyte-filtering capacity. The red pulp normally functions to filter erythrocytes and pathogens from circulating blood through open-ended capillaries lined with specialized endothelial cells and surrounded by reticular meshwork and resident macrophages. CMV infection results in marked disruption of normal splenic white and red pulp compartmentalization. The virus infects splenic stromal cells and endothelial cells, leading to transient reduction of CCL21 (a critical chemokine for splenic organization), which compromises the ability of lymphocytes to localize within appropriate T-cell zones [19].

The activation and expansion of marginal zone structures observed in this case likely represents early splenic immune response to CMV antigens: marginal zone macrophages and dendritic cells capture and present antigens to lymphocytes, initiating both innate and adaptive immune responses. However, the architectural disorganization suggests that CMV-induced inflammatory responses and cellular recruitment have overwhelmed normal splenic organization.

The distribution pattern of Bcl-2 expression has significant pathobiological implications.

Bcl-2, the founding member of the anti-apoptotic B-cell lymphoma family, prevents mitochondrial outer membrane permeabilization and caspase cascade activation, thereby blocking apoptosis through multiple mechanisms [20]. In normal thymic development, Bcl-2 expression is tightly regulated: DP thymocytes undergoing negative selection show low Bcl-2 expression, allowing apoptosis of autoreactive cells, while positively selected SP thymocytes and Tregs in the medulla express higher levels facilitating their survival [21].

The predominant medullary localization of Bcl-2 in this CMV-infected thymus raises important questions about how CMV affects thymic medullary development. CMV's known ability to upregulate Bcl-2 in infected cells suggests viral manipulation of medullary lymphocyte survival, potentially allowing survival of autoreactive or improperly selected thymocytes that would normally undergo apoptosis.

The preferential expression in marginal zones of the spleen is notable, as this compartment contains activated B

and T lymphocytes engaged in early immune responses. CMV-induced upregulation of Bcl-2 in marginal zone lymphocytes would promote survival of these activated cells, facilitating antibody production and cellular immune responses.

However, persistent Bcl-2 upregulation in the context of impaired p53 function could also prevent appropriate apoptosis of autoreactive or dysfunctional lymphoid cells, potentially contributing to abnormal splenic immune responses. The balance between protective anti-apoptotic signaling (facilitating anti-viral responses) and potential immune dysregulation (allowing autoreactive cell survival) represents a fundamental conflict during congenital CMV infection.

This weak p53 expression is consistent with CMV-mediated suppression of p53 functions through direct binding and transactivation inhibition by the viral IE2 protein, and potentially through other mechanisms [1, 22].

p53 normally functions as a critical regulator of selection processes in the thymus: in response to excessive TCR signaling or DNA damage signals, p53 triggers expression of pro-apoptotic Bcl-2 family members (Bax, PUMA, NOXA) and death receptors (Fas, TNF receptor), promoting apoptosis of improperly selected thymocytes [23]. The weak p53 expression observed in this case suggests impaired apoptosis signaling for eliminating autoreactive thymocytes, potentially contributing to abnormal T-cell repertoire generation.

Notably, CMV-mediated p53 suppression represents a fundamental molecular adaptation for persistent viral infection: p53-dependent apoptosis normally serves as an innate antiviral defense mechanism, inducing death of infected cells before productive viral replication completes. By suppressing p53, CMV promotes survival of infected cells and maximizes viral progeny production.

The combination of elevated Bcl-2 and reduced p53 activity creates a permissive intracellular environment markedly biased toward cell survival over apoptosis - a state beneficial for CMV replication but potentially harmful for normal thymic immune education processes.

The elevated Ki-67 expression in the cortex, particularly in subcapsular regions, suggests active proliferation of developing thymocytes despite architectural distortion. This is consistent with thymic hyperplasia (increased overall cell numbers and organ size) rather than thymic involution. The subcapsular zone normally contains cortical thymic epithelial cells and early CD4+CD8 – thymocyte precursors that have recently entered the thymus and are beginning TCR gene rearrangement and initial proliferation [24].

Elevated proliferation in this zone could reflect either: (1) normal developmental processes occurring despite concurrent infection, (2) compensatory proliferation attempting to replenish lymphocyte numbers lost to infection-induced apoptosis, or (3) CMV-driven proliferation of infected cells and recruited immune cells. CMV modulates cell cycle progression in infected cells to maximize availability of cellular DNA replication machinery, potentially affecting proliferation of infected thymic epithelial cells or resident myeloid cells within the thymus.

A central pathobiological consequence of CMV infection during thymic development is impairment of the critical thymic selection processes - positive and negative selection - that educate T lymphocytes and establish self-tolerance. CMV-induced disruption of thymic architecture, impaired p53-dependent apoptosis signaling for negative selection, and reduced capacity for generating regulatory T cells collectively impair thymic "learning."

PALS represent crucial sites of T-lymphocyte activation and proliferation in response to blood-borne antigens. The pronounced Ki-67 expression indicates active proliferation of splenic T lymphocytes, likely representing CMV-specific T cell responses attempting to control viral replication.

The enhanced proliferation in PALS regions is consistent with splenic CD8+ T cell expansion observed in congenital CMV infection, though these expanded T cells characteristically show reduced effector function due to T cell exhaustion mechanisms (PD-1+ expression, reduced IFN-γ and TNF-α production). The splenic CD8+ T cell response to CMV represents one of the few sites of robust adaptive immunity generation during congenital infection, likely aided by presentation of viral antigens by splenic dendritic cells and collaboration with maternal antibodies.

The profound effects of CMV on thymic and splenic development described in this case suggest significant disruption of adaptive immune system development.

Conclusion

This case of CMV infection during pregnancy with documented morphological changes in the fetal thymus and spleen illustrates the profound impact of this ubiquitous virus on developing immune organs. The enlarged thymus with preserved lymphocyte numbers but abnormal cortex-medulla ratio, combined with elevated anti-apoptotic Bcl-2 expression and reduced p53 function, suggests viral manipulation of thymic selection processes and impaired apoptosis signaling crucial for generating T-lymphocytes.

Similarly, the marked splenic white pulp hyperplasia with activation of marginal zone structures and pronounced Ki-67 expression in periarteriolar lymphoid tissue indicates vigorous splenic immune activation, yet compromised by architectural disorganization and likely functional exhaustion of CMV-specific lymphocytes.

At the molecular level, CMV-mediated modulation of BCL-2 family proteins (upregulated anti-apoptotic Bcl-2, downregulated pro-apoptotic functions) and suppression of p53 create a fundamentally altered cellular environment biased toward survival of infected cells and potentially dysregulated immune cells. This survival advantage for infected cells and impaired apoptosis of autoreactive or exhausted lymphocytes may explain the characteristic long-term sequelae of congenital CMV infection, particularly the persistent immunological dysfunction underlying susceptibility to secondary infections and late-appearing complications.

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