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Significant Elevation in Hepatic Enzymes After the First Dose of Alemtuzumab Treatment

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Abstract

There are many new treatments in Multiple Sclerosis (MS), such as monoclonal antibodies. We aimed to report the expected but crucial side effects of alemtuzumab treatment for the first time. A 32 years old female with MS had been received alemtuzumab; after therapy, 17-times increase of liver enzymes called fatal level was detected in blood tests. It could be caused by transient cell activation and infusion associated reactions (IARs). The side effects of monoclonal antibody treatments can be fatal to the patient, even if known.

Keywords: Multiple-sclerosis, Alemtuzumab, Side effect, Hypertransaminasemia

İlk Doz Alemtuzumab Tedavisinde Ciddi Karaciğer Enzim Yüksekliği

Öz

Multipl Skleroz'un (MS) yeni tedavileri arasında monoklonal antikorlar yerini almıştır. Bu olgu ile alemtuzumab tedavisinin beklenen ancak ilk kez hayati riske yol açan yan etkisini bildirmeyi amaçladık. MS tanısı ile alemtuzumab kullanan 32 yaşında kadın hastada, ilk doz tedavi sonrasında karaciğer enzimlerinde 17 kat düzeyinde önemli bir artış tespit edildi. Bu ciddi ve riskli durumun geçici hücre aktivasyonu ve infüzyonla ilişkili reaksiyonlardan (İİR'ler) kaynaklanabileceği düşünüldü. Monoklonal antikor tedavilerinin yan etkileri bilinmektedir ancak bu bilinen ve sık görülen yan etkiler bazı hastalarda hayati öneme sahip olabilir..

Anahtar Kelimeler: Multipl skleroz, Alemtuzumab, Yan etki, Hipertransaminazemi

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Introduction

Common side effects of alemtuzumab include infusion-related reactions and secondary autoimmune diseases. Liver side effects are generally considered to be rare, mild, and temporary (1,2). Although the efficacy of alemtuzumab has been reported in many studies, clinical trials are still needed for its safety. We report a patient developed infusion-related reactions accompanied by severe increase in liver enzymes after the first dose.

Case report

32 years old female patient had been diagnosed with Relapsing Remitting Multiple Sclerosis (RRMS) since 2004 after an optic neuritis (ON) attack. Cranial and cervical Magnetic Resonance Imaging (MRI) revealed lesions consisted with MS including periventricular, corpus callosum and cervical regions with minimal contrast enhancement on cranial era. In cerebrospinal fluid (CSF), IgG index was high and there were no oligoclonal bands. Three years later, she had another attack in her right eye and interferon beta 1b was started (other differential diagnoses such as neuromyelitis optica spectrum disorders, vasculitis were excluded). She was well on interferon-beta-1b therapy until 2011 and had no adverse effects from this drug.

However, she had two attacks in the following two years. Her neurological examination showed walking difficulties and dysarthria as sequela after high dose steroid regimens. She got gradually worse and started to slowly develop spasticity in the lower extremities although she was still able to walk independently (EDSS: 3.0). Due to getting worse gradually, fingolimod was started in 2015 with a diagnosis of progressive multiple sclerosis. Between 2015-2017, she had 4 severe (sensorial, spinal, cerebral) MS relapses (EDSS: 4.0). In February 2017 she got another clinical attack with right hemipharesis and received steroids without any contrast enhancement on MRI, but she was still going for worse afterwards with walking problems and frequent falls. In December 2017 she was decided to put on first dose alemtuzumab therapy because of clinical/radiological progression (Figure1).

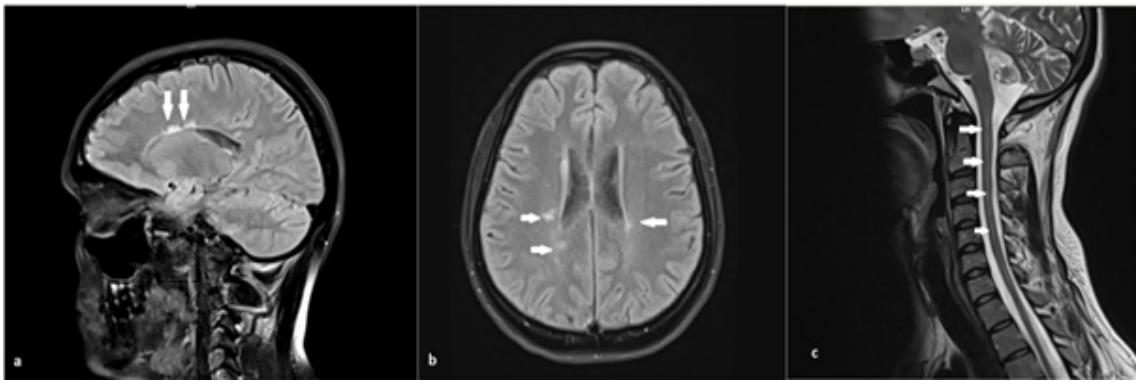

Figure 1. shows sections from the latest MRI of the patient. a. transverse b. longitudinal section of cranial MRI shows T2 hyperintense ovoid white lesions perpendicular to ventricles and on corpus callosum. c.T2 hyperintense merged lesions on cervical MRI.

The patient had no history of chronic liver disease or chronic alcohol use. All tests were normal before receiving alemtuzumab. 3 hours after starting to take alemtuzumab, paresthesia of the hands, fever, and parapheresis developed. Blood drawn at this point showed a 17-fold increase in AST; 15-fold increase in ALT (Table 1). Lymphocyte count was 30. After symptomatic therapy (antipyretic drug, hydration) in 3 hours her clinical symptoms disappeared, in 5 days laboratory testing got normal level. Other causes that increase liver enzyme (infections, exposure to substance, alcohol, other drugs) were excluded. Hepatic ultrasound (US) imaging was also normal after a few days. Due to vital side effect, alemtuzumab was stopped.

Discussion

Infusion-related reactions are common adverse effects with monoclonal antibodies. Adverse effects can be defined as signs or symptoms observed during administration of a drug or within 24 hours after that. Clinical presentation can range from mild discomfort to fatal events (3). Although the terminology for drug-induced hypersensitivity reactions is not standard and clear, there is a form of IAR called 'cytokine release syndrome (CRS)' defined by monoclonal antibodies. CRS is considered to be a result of activation of monocytes, macrophages, T cells and B cells, and is characterized by an increase in levels of TNFα and IFNγ within 1 to 2 h of stimulus exposure, followed by increases in interleukin (IL)-6 which was first detected at 4 hours in ex vivo study (4). A relatively more common presentation reported in literature is transient increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (5), however, underlying mechanisms are still not entirely clear. They are mostly described in long term follow-ups but one research studied the effects of alemtuzumab in the first week of treatment. They found less than 3x increase in ALT, AST and GGT on 3-5 days of treatment and they returned to normal values within 30 days (5).

Table 1. Summary of the patient's blood results from day 1 to day 5.

	First Day (before infusion)	**1. Day** (4 hours after infusion)	**2. day**	**3. day**	**4. day**	**5. day**	**Unit**	**Reference Range**
WBC	6.58	11.60	18.99	3.62	2.46	3.13	10^3/µL	4.1-11.2
Neutrophil	3.03	11.44	18.85	3.17	1.96	2.52	10^3/µL	1.56-6.13
Lymphocyte	2.88	0.03	0.03	0.09	0.03	0.09	10^3/µL	1.18-3.74
Monocyte	0.44	0.13	0.10	0.30	0.37	0.40	10^3/µL	0.24-0.36
Eosinophil	0.20	0.00	0.00	0.04	0.06	0.09	10^3/µL	0.04-0.36
Basophil	0.03	0.00	0.01	0.02	0.04	0.03	10^3/µL	0.01-0.08
Hematocrit	40.9	39.7	38.3	36	39.5	41.2	%	35.0-55.0
RBC	4.82	4.65	4.54	4.09	4.56	4.77	10^6/µL	4.0-6.20
Platelet	260	161	201	103	141	169	10^6/µL	150-500
AST	19.20	330	195	47	27.5	19.09	U/L	0-35
ALT	13.22	199	218	106.9	86.5	60	U/L	0-35
ALP	80.54	-	-	-	-	93.5	U/L	30-120
BUN	28	28	30.6	23.7	26.8	33	mg/dL	17-43
Creatinine	0.69	0.73	0.61	0.63	0.60	0.75	mg/dL	0.51-0.95
CK	43.7	48	41	24.8	18.8	16	U/L	0-145

ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CK: Creatinine kinase, WBC: White blood cell count, RBC: Red blood cell count

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Our patient's symptoms started 4 hours later than the start of infusion and resolved in 3 hours. Elevation of transaminases accompanied this presentation, so it is reasonable to consider this situation as a part of hypersensitivity reactions. Although we were not able to measure cytokine levels in this patient, these clinical pictures could be explained by CRS, considering timing, presence of hallmark symptoms such as pyrexia and transient worsening of neurological findings.

Although liver side effects are considered to be mild, transient and insignificant so far (3), ≥15 fold increase in liver enzymes is concerning and kept us from continuing with the drug. This condition can suggest a potential for causing life threatening liver failure, so we recommend clinicians to be aware of this potentially serious side effect and consider checking enzyme levels even after seemingly mild clinical reactions.

Conclusion

The side effects of monoclonal antibody treatments may be fatal to the patient, even if known. Liver enzyme monitoring should be performed before and after treatment. Our case is the first case in the literature with vitally high enzyme levels after alemtuzumab treatment.

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