FT136

LAD Cases

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Özet:
Lökosit adezyon defekti lökositlerin enfeksiyöz ajanlara cevap vermemesi, iltihap oluşmaması ve bozuk yara iyileşmesiyle karakterize nadir bir immün yetmezliktir. Bu konuşmada 2 LAD1 2 LAD3 hastasını anlatacağız. 4hastanın 3'ü Suriyeli ve akraba evliliği yapan ebeveynlere sahipler. Hastaların persistan enfeksiyon periyotları haricinde persistan lökositozlarıyla ön tanı konmuş ve akım sitometri ile konfirme edilmiştir. LAD3 hastalarında akım sitometride CD11abc Cd18 i mevcut olarak görülmüş ve adhezyon testi ile tanı konulmuştur. LAD 1 için ITGB2; LAD3 FERMT3 tarandı ve mutasyonlar gösterildi.4 hastanın 3 ü kemik iliği yapıldı. 1i vefat etti.

Abstract:
Leucocyte adhesion deficiency disease is a type of immunodeficiency resulted as loss of function to reaction to infectious disease, pus formation, disrupted wound healing. Here we report two LAD1 and two LAD3 with their clinical and functional analysis. 3 of 4 patients are Syrian origin and born into consanguineous families. Their diagnosis are made by flow cytometry and due to high leucocyte count. LAD3 patients have normal CD11abc CD18 levels so they're diagnosed by adhesion assay.Both confirmed with genetical mutations on ITGB2 and FERMT3. 3 of 4 underwent successful HSCT but one is unfortunately passed away.

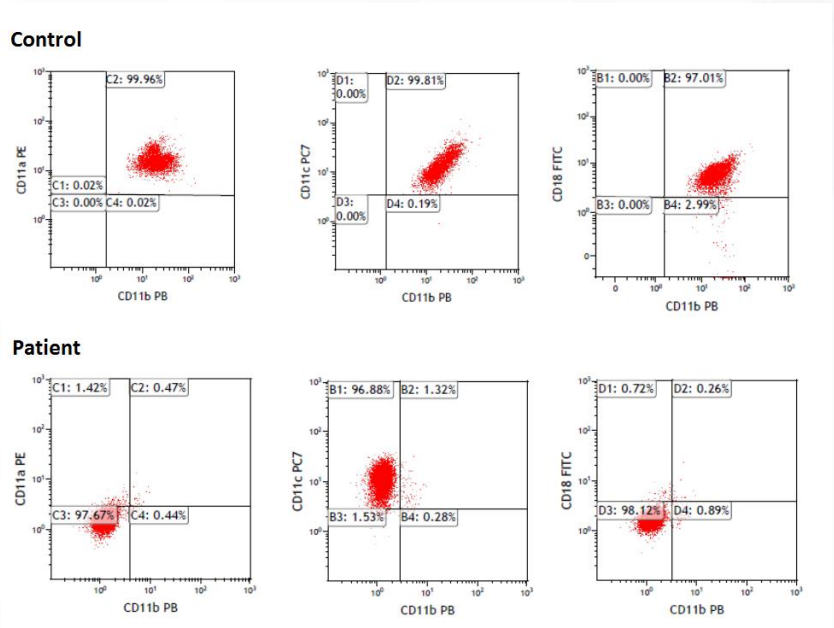
Cases with Leucocyte Adhesion Deficiency

LAD is a rare immundeficiency presented as; lack of adhesion ability of leucocytes to the inflammation sites. As a result; reaction to infectious disease, pus formation, wound healing is disrupted. LAD has three clinical forms called LAD1, LAD2 and LAD3 or 1 variant caused by the mutations in the genes following; ITGB2, SLC35C1, FERMT3 and defect in proteins;β integrins; GDP-fucose transporter; kindlin-3.[1] Patients with LAD mostly suffers from severe life threatening infections at the very early period of life, necrosis in the wound sites and delayed separation of umbilical cord.

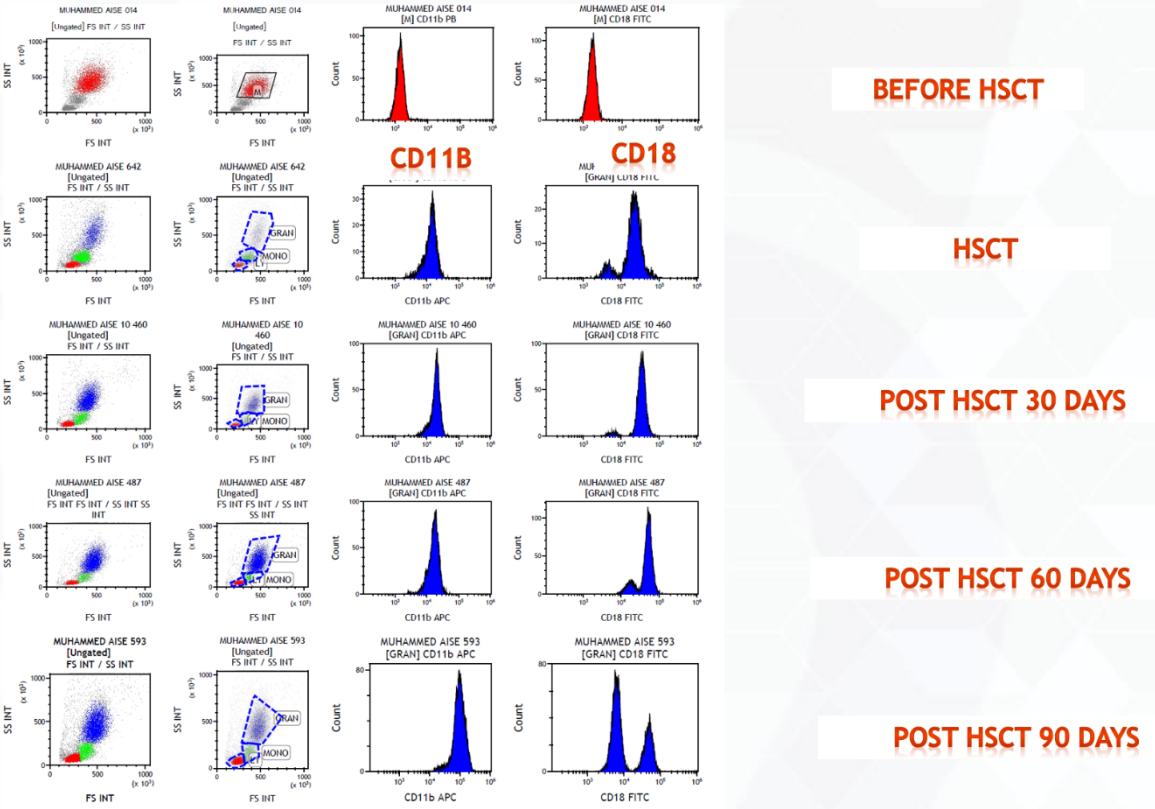
Table 1
Leukocyte adhesion deficiency

	Genetic defect	Clinical presentation	Diagnosis
LAD I	*ITGB2; encodes* CD18 subunit of β_2 integrins, resulting in impaired adhesion, chemotaxis, and neutrophil activation	Skin infection, soft tissue abscesses, delayed separation of umbilical cord and omphalitis, periodontal disease	Flow cytometry for CD11b/CD18 (Mac1)
LAD II	*SLC35C1*; encodes GDP-fucose transporter 1, resulting in impaired expression of fucosylated proteins, including SLeX ligand for selectins	Similar infections to LAD I but not as severe; developmental delay, short stature	Flow cytometry for leukocyteCD15s (SLeX) Bombay (hh) phenotype in red blood cell typing
LAD III	*FERMT3*; encodes kindlin-3, resulting in defective integrin activation and impaired leukocyte and platelet adhesion	Similar to LAD I; also bleeding tendency	Functional assays for neutrophil and platelet adhesion

LAD cases generally suspected by high leucocyte count at first. Then to show absence of CD11abc CD18 CD15 by flowcytometry works for diagnosis of LAD 1 and LAD2.
2 of the our cases are LAD1 which is relatively frequent. Both patients are from Syrian origin and have the same mutation in ITGB2 gene but not known relation between families. Both family has a child loss previously in early age of life. Also marriages are consanguineus.
First M.A. patient had a pneumonia during newborn period but revealed with intravenous antimicrobial therapy. At 7-8 months old repeated severe purulent otitis media and high leucocyte count (40000-10000) brought to the mind LAD. And first step flow cytometric analyse showed absence of CD18, CD11a expression and CD11b apparently CD11c partly. Then patient had laparatomy due to abdominal tenderness surprisingly **abcess formation** is seen and his operation scar healed **without necrosis.** Patient underwent HSCT and surviving now.
Second A.H. had repeated severe pneumonia story newborn to 4months old and at 4 months old he needed ICU care wbc count was 97100 and LAD1 showed by flowcytometric analysis. He survived until 4 years old by prophilaxis. He underwent HSCT from full match mom.
Our other cases are LAD3 which is pretty much rare. Until now approx. *300 patients were submitted. Most of the patients are from Middleeastern countries.* LAD3 patients need eritrocyte or thrombocyte support and as a differential diagnosis by flowcytometry we show presence of CD11abc CD18 CD15.

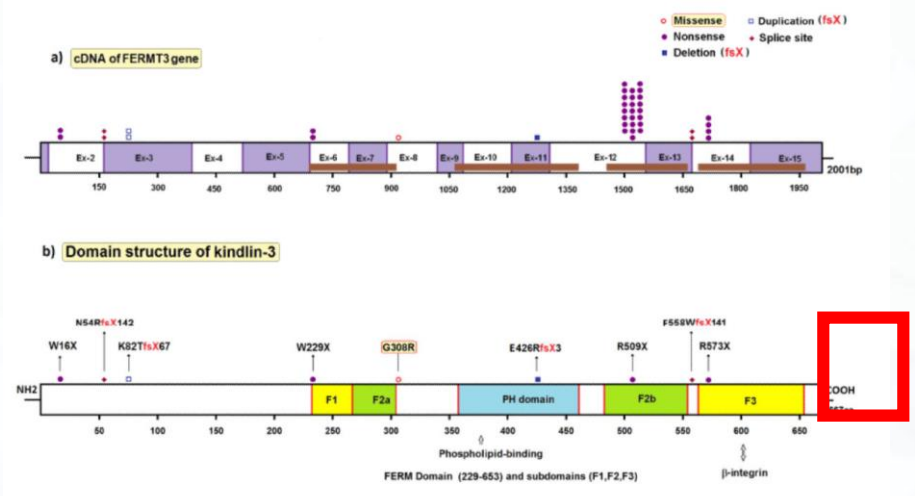


Şekil 3 Patient 1 M.A 's flow cytometric analysis comparing the control, patient lack of CD11ab CD18 but partially present Cd11c



Şekil 4 Patient 1 M.A. follow up after HSCT for chimerism

First LAD3 patient Ö.D. is 6 months old. he had severe pneumonia since newborn period . he was under followup in ICU, leucocyte count was 38800. Patient also received 3 times eritrocyte suspension and 3 times platelet suspension due to gastrointestinal bleeding.
He is suspected as LAD but CD11abc CD18 CD 15 was present with Flow cytometry so for LAD3 as a result of detailed research mutation found in FERMT3 gene and lack of adhesion ability was shown.
The other LAD3 patient A.G. also had a sibling death story. Syrian origin. Consanguineus marriage. Since newborn period patient had infectious problem and high leucocyte count. Patient also needed eritrocyte and platelet transfusions 3-5 times. LAD3 suspicion lead us to sequence FERMT3 gene and a known mutation forTurkish patients c.1525C>T exon 12 p.Arg509X (Kuijpers TW, 2009). We also sequenced patient's another alive brother and he was not a carrier so he underwent HSCTfrom that brother.



Patient 1: Flow cytometric analysis of leucocyte adhesion molecules with specific antibodies CD11b, CD11a, CD11c.

Sources:

1. *Van de Vijver, Edith, et al. "Hematologically important mutations: leukocyte adhesion deficiency (first update)." Blood Cells, Molecules, and Diseases 48.1 (2012): 53-61.*
2. *Hanna, Suhair, and Amos Etzioni. "Leukocyte adhesion deficiencies." Annals of the New York Academy of Sciences 1250.1 (2012): 50-55.*
3. *Bunting, Michaeline, et al. "Leukocyte adhesion deficiency syndromes: adhesion and tethering defects involving β 2 integrins and selectin ligands." Current opinion in hematology 9.1 (2002): 30-35.*