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A Rare Case of HLA2B27 Positive Presenting with Spondyloarthreditis and Enthesial Inflammation with Negative Rheumatoid Factor, ANA, who Responded to Methyl Prednisolone along with Hydroxychloroquine

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Abstract

HLAB27 related conditions represents a group of HLA-B27 associated disorders that are HLA-B27 related uveitis and members of the spondyloarthritides which include reactive arthritis, psoriatic arthritis, and Ankylosing Spondylitis (AS). The spondyloarthropathies have the properties of implication of the axial spine, besides the non articular involvements of the uvea as uveitis, association of psoariasis, inflammation of the aortic root, as well as inflammation of the intestine This is the presentation of an atypical case that was not typical case of AS which is usually associated with HLAB27 related arthritis but presented with symptoms of spondyloarthritides like reactive arthritis, venous involvement, without uveitis, psoariasis, or gut involvement with positive HLAB27 but negative Rheumatoid Factor (RF), Anti Nuclear Factor (ANA) although high hsCRP and ESR with marked incapacitating pain

making her immobile that improved with bolus methyl prednisolone and Hydroxychloroquine (HCQ).

Keywords

HLA-B27; Spondyloarthritides; Rheumatoid factor; Anti nuclear factor; hsCRP methyl prednisolone; Hydroxychloroquine

Abbreviations

AS: Ankylosing Spondylitis; RF: Rheumatoid Factor; ANA: Anti Nuclear Factor; HCQ: Hydroxychloroquine; MRI: Magnetic Resonance Imaging

Introduction

Spondyloarthritides represents a group of inflammatory disorders that have in common a correlation with the MHC class I molecule, HLA-B27. Having the knowledge of this correlation, these diseases are traditionally believed to represent aberrations of adaptive immunity. Nevertheless, recent data are questioning this presumption and evoking the probability that innate immunity might be more significant as far as etiopathogenesis is considered as compared to earlier researchers (Figure 1). Here we present a case report of a patient who had persistent pains with rheumatoid factor (RF) negative but HLAB27 positive who responded to bolus methyl prednisolone after depotmedral and then responded to wysolne with hydroxychloroquine 400 mg bd along with dabigartan.

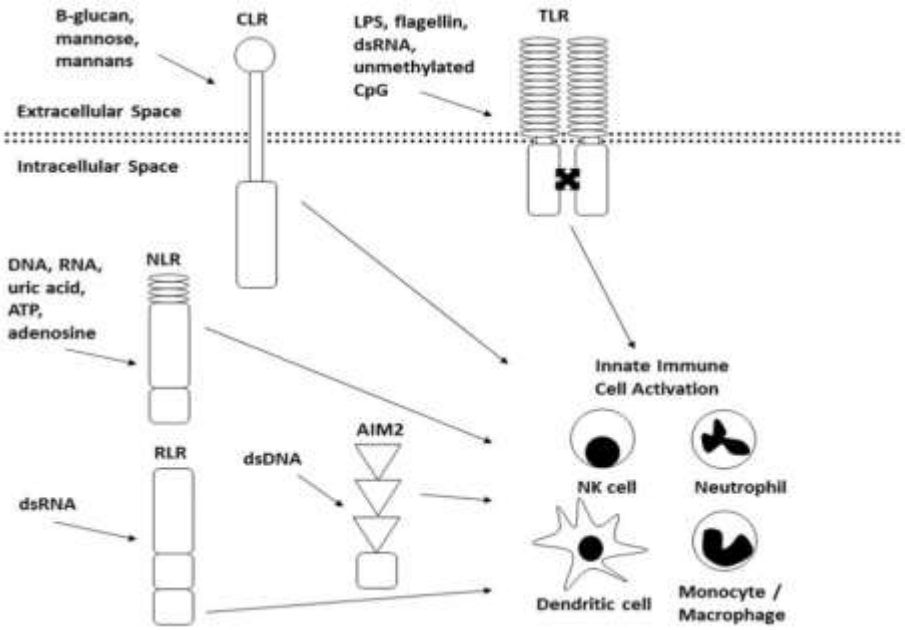

Figure 1: Courtesy activation of innate immunity [23].
MAMPs and DAMPs activate CLRs, TLRs, NLRs, RLRs, and AIM-2 resulting in activation of innate immune cells including NK cells, neutrophils, monocytes/macrophages, and dendritic cells.

Case Report

A 44 year old patient married for 20 years P2, Last child birth 18 yrs back presented with history of severe pain in knees along with varicose veins or feeling of clots like feeling in lower legs, pain along with stiffness of knees for the last 2 years ,that had worsened markedly now with inability to walk, sit. Her cycles were regular 3-4/30 days.

On General Physical Examination her height was 152 cm weight -52kg, body mass index (BMI), 22Kg/$m^{2,}$, BP was 110/70 mm Hg, varicosities were present on the lower limbs. No tenderness was there on back, knees were not swollen. Investigations were as following for haemogram, escalated CRP & hs CRP, Normal Thyroid function tests other than borderline T4 increased although normal TSH, ESR borderline increased, Negative HIV, HBsAg & HCV (Table 1). Table 2 showing normal Rheumatoid factor, ANA negative, increased hsCRP, negative anti CCP but positive HLA B27, Table 3 showing report of Bone Mineral Density Densitogram test correlating with osteoporosis-figure2 although she was a premenopausal patient, MRI spine normal with no involvement of sacroiliac joints along with lumbar spine or rest of spine, normal Doppler scan of blood vessels of limbs.

Number	Investigation	20/6/19	20/9/19	11/1/2020
1	Haemoglobin	13.70g	12.90g	11.70g
2	TLC	6650	6140	6640
3	DLC	P63L32M3E2	P66L20M5E5	P72L33M2E3
4	ESR	14	42	37
5	Platelets	3.65lacs/cumm	3.45 lacs/cumm	3.49 lacs/cumm
6	Urea		39mg	31.8mg
7	Creatinine	0.79mg	0.74mg	0.70mg
8	CRP	4.71	8.44	-
9	Cholesterol	-	228	
10	Triglycerides	-	150	-
11	HDL	-	48	-
12	LDL	-	150	-
13	VLDL	-	30	-
14	Hiv/HbSAg/HCV	-	-	nonreactive
15	T3/T4/TSH	2.33/156/2.65(nmol/l&Uiu/ml	-	-

Table 1: Investigations.

Number	Investigation	9/3/2020	31/5/20
1	RF	9.81(<20	9.18U
2	hsCRP	11.24(high risk>3ng/L)	-
3	ANA	Negative	-
4	AntiCCP	1.5	1.5
5	HLA B27(PCR)	Positive	-

Table 2: Investigations continued.

Reference DB	Asia	Young Adult	77.00%
OI	38.3	Age Matched	83.70%
SOS	1567.8m/s	OPR	N/A
T Score	-2.28	Z Score	-1.49%

Table 3: Ultrasound bone mineral densitometry diagnosis system.

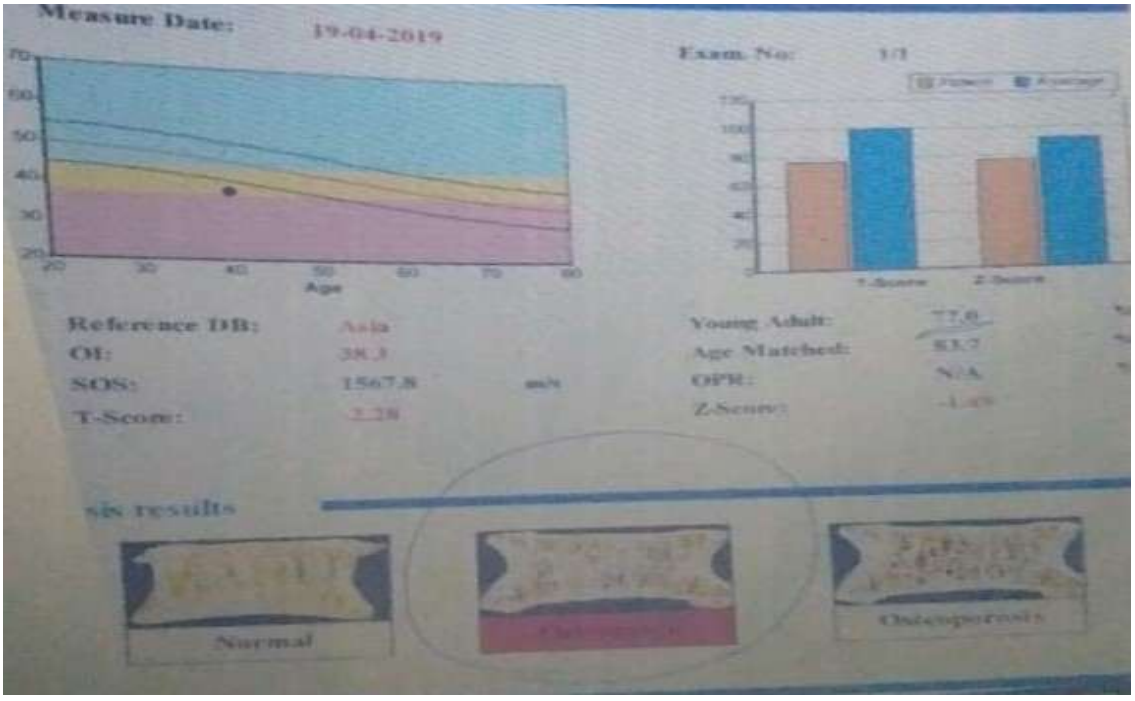

Figure 2: Showing the Bone mineral density diagnosis system assesment for osteoporosis severity revealing presence of osteoporosis middle picture.

Magnetic Resonance Imaging (MRI) Sacroiliac Joints-no obvious discernible abnormality seen, along with earlier MRI of full lumbar, thoracic spine being normal. No disc problems were seen. Doppler studies showed no valvular abnormalities in the venous system.

Treatment

After receiving a lot of non-steroidal anti-inflammatory drugs (NSAIDS), daphlon 500mg bd, foot stockings, crepe bandage with no relief to the patient, the initial treating rheumatologist was reluctant to start any specific therapy .With the total incapacitation we decided to administer injection depot medral 160mg in view of injectionmethyl prednisolone 120 mg injection being not available at that time period and then put her on wysolone 10mg daily, along with dabigatran 110mg daily and sulfasalazine 500mg bddespite negative Rheumatoid factor , but since sudden aggravation of pain was there again 1 month following depotmedral, methyl prednisolone 120mg intravenous bolus followed by replacement of sulfasalazine with Hydroxychloroquine 400mg bd was done besides continuation of wysolone 10mg, along with the anticoagulant dabigatran following which she has improved considerably with all incapacity finished and good quality of life (QOL), with movements improved, walking and working normally. She has been followed subsequently for 6 months and is pain free on same medicine now.

Discussion

HLA-B27 correlated conditions are HLA-B27 associated uveitis as well as members of the spondyloarthritides that are reactive arthritis, psoriatic arthritis, as well as Ankylosing Spondylitis (AS). HLA, basically belongs to the MHC Class 1 surface encoded by the MHCB gene on chromosome 6 awa is the maximum necessary gene which makes an individual susceptible to AS. HLA-B27 presents peptide antigens to T immunocytes of the human body defense processes as well as is believed to be significantly associated to AS as well as correlated inflammatory diseases. A review conducted involving greater than 7500 peptides that got presented by the 8 commonest HLA-B27- allotypes (HLA-B27-02-HLA-B27-09) pointed that there was binding as per consensus as well as selection motifs, demonstrated important similarities as well as variations among different HLA-B27- allotypes [1]. Further a spectrometry study did a review where a huge amount of HLA-B27-repository which might be more specific to origination as well as propagation [1]. Certain microbial peptides have similarity to the self peptides present within our body tissues as well as have the ability of stimulating response of certain HLA-B27-particular CD 8+T lymphocytes. There is a reaction of the T lymphocytes with these HLA-B27-peptide complexes resulting in autoreactivity as well as autoimmune disease [2,3]. That cartilage, specifically, the proteoglycan aggrecan, is the particular immunological target in SpA has been pointed [4], nevertheless, present studies over these peptides just got results that were not consistent. Additionally, rats possessing HLA-B27- particular CD 8+T lymphocytes still develop AS, that points that greater peptides which further need to be unrevelled [5]. Pul-D liberated pullulanase have the ability to interact with antibodies which associate HLA-B27 as well as myosin, whereas Pul-A components might interact with type I, III as well as IV collagens [6], that gives evidence for the reason molecular mimicry hypothesis might be right. Particular cross reactions stimulate the antibacterial antibodies which associate the HLA- molecules on immunocytes, chondrocytes as well as fibroblasts [7], that stimulate a cascade involving inflammatory reactions with the quantity of cytokines, complement proteins,

proteinases as well as the similar formed [8]. The common spondyloarthropathies have the properties of implication of the axial spine, joints present in the periphery, as well as enthesial inflammation besides the non articular involvements of the uvea as uveitis, association of psoariasis, inflammation of the aortic root as well as inflammation of the intestine [9]. The correlation with HLA-B27 is greater than 90% of patients in the United Kingdom with Ankylosing Spondylitis (AS) [10], despite not all subtypes being correlated with disease [11]. Other HLA-B27 associations include reactive arthritis (67%) [10], IBD-associated spondyloarthritis (72%) [12], psoriatic arthritis-both peripheral and axial (24-90%) [13], juvenile enthesitis-related arthritis (76%) [14], and acute anterior uveitis (52%) [15]. Our patient did not have any uveitis, psoariasis or any associated inflammatory bowel disease (IBD). ECG was normal with normal BP but her marked varicose veins like symptoms with normal venous valves on Doppler point to enthesial inflammation in a case who had HLAB27 positive. No other family member had similar problem. Despite HLAB27 being positive, as well as raised hsCRP, in view of negative Rheumatoid factor (RF), antinucleic acids (ANA), no rheumatologist started any therapy. Since poor response has been observed with rituximab (pre B cell) and abatacept (costimulation blockade) [16,17] in terms of improving spondyloarthritides and pain relief they have not proven to be successful in terms of adaptive immunity. IL-17 as well as IL-23 inhibitors have shown some response in psoariasis associated problems but our patient did not have psoriasis [18], Similarly IL-1 inhibitors like anakinra [19] has been tried but still queries are there and TNF Inhibitors also have not worked [20]. Although lot of monoclonal antibodies [21,22] are being studied they turn out to be very expensive. A lot of controversy has been there regarding involvement of innate immune response or adaptive immunity in HLAB27 [23]. Here our patient is an example of overlapping spondyloarthrides with HLA-27 positive thus we decided to try drugs commonly utilized for RA with response to usual drugs used for Rheumatoid arthritis(RA) and our patient responded to methyl prednisolone followed by hydroxychloroquine and maintainance dose of wysolone along with simple oral anticoagulant like drug like dabigatran. This case exemplifies how many cases of HLAB27 positive spondyloarthropathies suffer with no proper therapy available currently although lot of trials are ongoing to study the etiopathogenesis be it involvement of microbes, arthrogenic peptide theory, homodimerization theory or ER mis-folding or UPR, GWAS involvement as well as other suggestions. Lot of work is being done on this to pinpoint if it is innate or adaptive immunity involvement and find out specific therapies for this intriguing problem [23].

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