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REVIEW ARTICLE

HAEMATOLOGICAL INVESTIGATIONS IN AUTOIMMUNE DISEASES WITH ORAL MANIFESTSTIONS-A GUIDE TO ORAL PHYSICIANS

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ABSTRACT

The environment contains various microbial agents that have potential of causing diseases. Immunity plays an important role of protecting body from various causative agents by recognizing foreign agent and eliminating them from the body but sometimes these immune system acts against self-antigens. Thus, resulting into auto-immune diseases which affects multiple organs including oral cavity. Knowledge of these diseases is not only important to diagnose the diseases but also helps in treatment. This review was undertaken to highlight the hematological investigations used to assess the autoimmune diseases presented with oral manifestations.

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INTRODUCTION

Immune system is a multidimensional system which plays important role in protecting the body against infection by counter-attacking the insults from the environment. Once a branch of microbiology, immunology has grown into one of the principal sciences of human diseases which has further enhanced the understanding of the disease process providing tools for investigation of various clinical conditions. The treasure of knowledge has led to development of various diagnostic tests and treatment which targets the disease process. The term autoimmune disease refers to a disorder in which there is evidence of an immune response against self. Autoimmune diseases may occur primarily due to either antibodies (autoantibodies) or immune cells, but a common characteristic of this disease is the presence of a lymphocytic infiltration in the target organs (Greenberg, 2003). Autoimmune diseases like Systemic lupus erythematosus (SLE), Systemic sclerosis and Sjögren's syndrome affects multiple organs and also shows oral manifestations.

Systemic lupus erythematosus (sle): Systemic lupus erythematosus (SLE) is a complicated and multifactorial interaction among various genetic and environmental factors affecting multiple systems and is characterized by production of pathogenic autoantibodies which are directed against nucleic acids and their binding proteins that predominately affects women of the reproductive age (Birtane, 2012; Antinuclear antibody testing, ?). SLE is characterized by production of several antibodies against self –antigens or environmental-antigens on surface of B cells which process the antigen into peptides and present them to T-cells.The activated T cells stimulate B cells to produce pathogenic autoantibodies (Lennette's laboratory diagnosis of viral infections, 2016). The exact etiology of SLE is unknown though several factors like genetics, drugs like sulfasalazine and viruses like Epstein-Barr virus, cytomegalovirus, varicella-zoster are considered as contributing factors (Greenberg, 2003).

Sclerodermap: Scleroderma also known as systemic sclerosis is systemic multi organ autoimmune disorder characterized by hardening of skin.[1]the term scleroderma, derived from the Greek words for hard and skin, is used to describe a group of clinical disorders characterized by thickening and fibrosis of the skin. Risk is higher in women than men and peak in individuals aged 30-50 years. It has no definitive treatment. It may be limited or diffuse depending upon manifestations of symptoms or signs affecting internal organs especially lungs, heart, or kidney (Ingegnoli, 2013). Systemic sclerosis involves abnormalities of the immune and vascular systems, where in genetic, infections and environmental factors play a key role in

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Table 1. Clinical and oral manifestations of autoimmune diseases

ORGAN	SLE		SCLERODERMA	
	SYMPTOMS	PATHOGENESIS	SYMPTOMS	PATHOGENESIS
RENAL (Greenberg, 2003; Manifestations of Systemic Lupus)	Nephrotic Syndrome	Deposition of immuncomplexes in the basement membrane of glomerulus results in destruction of glomerulus due to glomerulonephritis	Hypertension	Interlobular arteries are affected arteries show intimal proliferation with luminal occlusion.
CARDIAC/ HEART[1, 9]	Verrucous Valvular Lesions	Accerlated atherosclerosis and valvular heart diseases affecting endocardium	Pericarditis, arrhythmias, and congestive heart failure	Hypertension due to blood vessel occlusion and and atherosclerosis,degeneration of myocardial fibers which are replaced by fibrosis
BLOOD CELLS and VESSELS (Greenberg, 2003; Manifestations of Systemic Lupus)	Leukopenia	Due to immunosuppresive therapies	Fibrosis affects multiple organs	Larger blood vessels display intimal proliferation, lumenal occlusion and fibrosis.
	Anaemia	Anaemia is present due to long term disease activity and haemodialysis	Raynaud's phenomenon/ digital ischaemic-fingers turn white, then blue, then red in response to cold exposure or emotional stress-	Small vessel shows endothelial and platelet activation resulting in release of the vasoconstrictors and immune cells which causes intimal hyperplasia leading to vasculopathy and tissue ischemia.
	Thromobo-cytopenia	Increased phagocytosis of auto-antibody coated platelets by spleen, liver, bone marrow.		
SKIN[1, 9]	Butterfly or malar rash-	Exacerbated by ultra-violet lighta erythematous rash noted on cheeks and bridge of nose, involving chin & ears	Early sign-puffiness, swelling and decreased flexibility of the joints and tendons	Collagen increases in a homogeneous, hyalinised pattern and extends from the papillary dermis to the subcutis. Increased collagen replaces subcutaneous fat and surrounding atrophic sweat gland causing thickening of skin.
			Later stages-shiny, taut and thickened skin with hyperpigmentation, giving a salt-and-pepper appearance.	
ORAL MUCOSA (Greenberg, 2003; Manifestations of Systemic Lupus)	Annular Leukoplakic areas	Lesions are ulcerated areas with white small dots surrounded by small radiating white striae composed of keratinised border.	Mask like face appears due to loss of skin folds.	
	Erythematous erosions	Also known as Chronic ulceration resembles lichen planus arecaused by Vasculitis	Tongue appears hard and rigid leading to difficulty in speaking and swallowing.	
	Xerostomia, dental caries and candidiasis-	Present in patients treated with steroids or immunosuppressive agents	Oral telangiectasia on hard palate and lips	
	Glossodynia, Dysgeusia, Dysphagia, dry mouth, mucositis	Secondary to Vasculitis	Angle of mandible resorption due to involved masseter muscle, resorption of coronoid and condylar process due to involvement of digastric muscle	
			Radiographically, calcinosis and thickening of periodontal space is observed.	
			Drug induced-gingival hyperplasia	
Gastro-intestinal			Dysphagia,retrosternal burning pain and acid regurgitation, Chronic esophagitis can cause Barrett's esophagus	GIT affected by smooth muscle atrophy and fibrosis
Musculo-skeletal			Pain,, muscle weakness, arthritis, tendonitis and joint contractures	Myopathy,synovitis
Pulmonary			Dyspnea and nonproductive cough, interstitial lung disease, pulmonary hypertension, pleuritis and pleural effusion, and aspiration pneumonia	Thickening of the alveolar septae along with pulmonary fibrosis

Table 2. Investigations

Investigations	Normal Values	Inferences		
		Sle	Scleroderma	Sjogren's Syndrome
Haemoglobin (Greenberg, 2003; Sembulingam, 2012)	Average haemoglobin (Hb) content in blood is 14 to 16 g/Dl	(Decreased) Anaemia	(Decreased) Anaemia - iron deficiency anemia is seen; due to chronic bleeding in the gut from esophagitis or watermelon stomach or other telangiectasia	Normal
Complete blood count-differential wbc count (Greenberg, 2003; Sembulingam, 2012)	NEUTROPHILS-50 to 70% LYMPHOCYTES-20 to 30 %	Leukopenia (decrease in lymphocytes, neutropenia)	Increased in scleroderma	Normal
Platelet count (Greenberg, 2003; Sembulingam, 2012)	150,000 to450,000/mm3	Thrombocytopenia (decreased)	high frequency of antinuclear antibodies 90–96% -positive	Normal
Erythrocyte sedimentation rate (Greenberg, 2003)	By Wintrobe Method males : 0 to 9 mm in 1 hour In females : 0 to 15 mm in 1 hour Infants : 0 to 5 mm in 1 hour	INCREASED in systemic lupus erythematous	Positive	Normal
Antinuclear antibody (ana) testing (Antinuclear antibody testing, ?; Greidinger 2003)	ANA titers at or above 1:320 are considered positive	high frequency of antinuclear antibodies	Normal	high frequency of antinuclear antibodies
Rheumatoid antibody (igm rheumatoid factor) (Singh, 2011)	Present in 5–30% cases of SLE	Positive	Normal	
Double-stranded dna antibody (Provan, 2009)	Present in 60% cases of SLE			
Rnp (Provan, 2009)	Specific for SLE			
ANTI-SCL-70 [8]			Positive	
anti-SSA/SSB (Sjogren's syndrome A antigen/Sjögren's syndrome B antigen) (anti-Ro/La)[64]				Positive

causing vascular injury which alters vasodilator/ vasoconstrictor balance resulting into impaired blood flow response causing ischemia–reperfusion episodes leading to oxidative stress that increases vascular injury which further causes fibrosis of end organs (Mok, 2003; The Pathogenesis of Systemic Lupus Erythematosus, ?; Achour *et al*., 2012).

Mikulicz's Disease: Mikulicz's disease, previously known as benign lymphoepithelial lesion, is characterized by symmetric lacrimal, parotid, and submandibular gland enlargement with associated lymphocytic infiltrations. Mikulicz's disease is associated with prominent infiltration of igG4-positive plasmacytes into involved exocrine glands (Greenberg, 2003). Mikulicz's disease is associated with prominent infiltration of IgG4-positive plasmacytes into involved exocrine glands (Manifestations of Systemic Lupus Erythematosus).

Sjögren's Syndrome: Sjögren's syndrome is a chronic autoimmune disease characterized by symptoms of oral and ocular dryness, exocrine dysfunction and lymphocytic infiltration, and destruction of the exocrine glands. The salivary and lacrimal glands are primarily affected, but Sjögren's syndrome is a systemic disorder, and dryness may affect other mucosal areas (nose, throat, trachea and vagina) and the skin and involve many organ systems (thyroid, lung, kidney, etc.). Sjögren's syndrome patients also frequently experience arthralgias, myalgias, peripheral neuropathies, and rashes (Greenberg, 2003; Sembulingam, 2012). The most common hematological investigations undertaken to assess these autoimmune diseases are as follows- Antinuclear Antibody (Ana) Testing, Rheumatoid Antibody, Double-Stranded DNA Antibody, RNP (Ribonucleic Protein).

Significance of the test

Antinuclear antibody (ana) testing: Antinuclear antibodies (ANA) usually target specific antigens in the nuclear part of the cell, although they can sometimes show affinity against all types of subcellular structures and cell organelles, including the cytoplasm, nuclei, nucleoli, or cell surfaces. Patients with SLE have unknown cells present in their bone marrow which are called Lupus Erythematosus (LE) cells. These cells are polymorphonuclear leukocytes which have capability to phagocyte the bare nuclei of other leukocytes with the help of auto antibodies thus providing opsonization to the liberated nuclear material of the target cell. ANA helps to detect LE cells in SLE.[4] ANA is 95% of the times positive in SLE and scleroderma but anti Scl-70 is specific, while 70% of the times ANA is positive in Sjögren's syndrome (Ingegnoli, 2013; Greidinger, 2003; Singh, 2011).

Rheumatoid Antibody: Infections and chronic diseases may be characterized by the presence of serum rheumatoid antibodies. The ability of rheumatoid antibodies to increase the clearance of immune complexes and produce B cells that may behave as antigen-presenting cells (APCs) and aid the immune response against the antigens (Lennette's, 2016).

Double-stranded dna antibody: anti-DNA antibodies bind to a conserved nucleic acid determinant widely present on DNA. Anti-DNA antibody titers frequently vary over time. Anti-DNA antibodies differ in their properties, including isotype, ability to fix complement, and capacity to bind to the glomeruli causing pathogenicity (Ingegnoli, 2013). RNP (Ribonucleic Protein): the levels of autoantibodies against nucleic acid auto-antigens (particularly RNA-proteins) is markedly higher than

autoantibodies against non-nucleic acid associated auto-antigens (Mok, 2003). Hence, this article is an attempt to elaborate hematological investigations undertaken to assess the autoimmune diseases presented with oral manifestations to help clinician in diagnosis and treatment planning.

Conclusion

Oral health is an integral part of total health, and oral health care professionals must adapt to demographic changes and medical advances and shoulder the responsibility of being part of the patient's overall health care team. An apparently fit patient seeking dental treatment may have a serious underlying systemic disease, which can significantly affect the course of dental management so an appropriate medical history and investigations play an important role in recognition of the classic presentation of signs and symptoms, important to diagnose the underlying disease. Hematological investigations provide a wealth of important information which can assist the oral physician in patient diagnosis and management as the oral cavity.

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