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September 02, 2024

Parameter	**Value**	**Reference Range**
Haemoglobin	**10.34 gm/dl**	**11-15 gm/dl**
Total WBC count	**10900/cumm**	**4000-11000/cumm**
Platelet count	**158000/cumm**	**1.5-4.1 L/cumm**
ESR	**50 mm**	**0-19 mm**
Biochemistry		
Urea	**19 mg/dl**	**14-40 mg/dl**
Creatinine	**0.7 mg/dl**	**0.6 to 1.2 mg/dl**
Total bilirubin	**0.8 mg/dl**	**0.1-1.2 mg/dl**
Total Creatinine Phosphokinase(CPK)	**464 IU/L**	**0-145 IU/L**
Thyroid Profile		
Free T3	**1.69 pg/ml**	**2-4.4 pg/ml**
Free T4	**1.32 ng/ml**	**0.93-1.7 ng/ml**
TSH	**22.99 µIU/ml**	**0.27-4.2 µIU/ml**
Anti- TPO antibody	**<5 IU/ml**	**0-35 IU/ml**

Title :

"Multisystemic Complications and Rapid Decline in Anti-MDA-5 Positive Amyopathic Dermatomyositis: A Case Study"

Abstract :

The term "clinically amyopathic dermatomyositis" was first introduced by Pearson in the 1960s to differentiate individuals exhibiting typical skin features of dermatomyositis but lacking clinical evidence of myositis. Clinically, there are two types of amyopathic dermatomyositis (CADM): amyopathic DM and hypo myopathic DM. Interstitial Lung Disease(ILD) is regarded as a frequent serious consequence, with a 5-65% documented prevalence. Anti-melanoma differentiation-associated gene 5 (MDA-5) is a specific autoantibody that is positive in a fraction of individuals with CADM. Glucocorticoids are the initial treatment choice while immunomodulators can be used in refractory cases. In our case,60-year-old female patient with complaints of cough, breathlessness and fever was MDA-5 positive with multiple hyperpigmented skin lesions over hands ,face and chest, painful oral ulcers, elevated total creatinine phosphokinase(CPK), elevated ESR and positive ANA and Ro-52 and received the treatment with mycophenolate mofetil, prednisolone, dextromethorphan syrup, rituximab, cyclophosphamide, and tacrolimus.

Introduction :

Among the several forms of dermatomyositis, clinically amyopathic dermatomyositis(CADM) is a rare condition with an annual incidence of 2.08 per million people[7] and comprise about 20% of the total DM population. CADM refers to the group of patients with biopsy proven cutaneous findings of DM that never manifest clinical weakness or markedly elevated muscle enzymes, but may have subclinical muscle abnormalities on electromyogram, MRI, or muscle biopsy studies. MDA-5 antibody positivity has been linked to a high incidence of ILD (90–95%) in CADM patients, especially RP-ILD (50–80%)[1,5], MDA-5 have prevalence of 0-13% in caucasians, 11-57% in Asians and 7-12% in juvenile DM. Limited understanding exists regarding the pathogenic mechanisms of anti-MDA5 DM due to its rarity, although it is thought to result from specific gene-environment interactions, with documented HLA allele associations in Asian populations.[2] Gottron's sign and papules are the pathognomonic cutaneous lesions associated with dermatomyositis.[6] Early administration of a treatment regimen combining high doses of

systemic glucocorticoids with other immunosuppressive medications like calcineurin inhibitors and/or cyclophosphamide seems to offer the best chances of survival for individuals with CADM associated with RP-ILD, whereas for refractory disease, further treatments like plasma exchange can be introduced.[3,4]

Case Report:

A 60-year-old female patient presented with complaints of dry cough since 2 months, breathlessness on exertion since last 15 days and fever since 5 days. There was no complaint of exposure to allergens, weight loss, dyspepsia, pedal oedema , orthopnea, chest pain, decreased urine output, muscle weakness or joint pain. Patient had a past history of multiple skin lesions over hands, face, chest, shoulder and gluteal region since last 6 months and oral ulcers for 3 months for which she received medications but her symptoms continued to worsen. On general examination, respiratory rate was 26/ minute and oxygen saturation was 94%(for which she was given nasal O2), while other vitals were stable. On head to toe examination, violaceous erythematous rash(Heliotrope rash) involving periorbital region, Gottron papules over metacarpophalangeal and proximal interphalangeal joint, plaques over extensor surface of elbow(Gottron sign) and erythema over front of neck and back, were observed which strongly suggested clinical finding of dermatomyositis.

Despite repeated enquiry, the patient denied having muscle pain or weakness ever, and there was no objective evidence of decreased muscle power on CNS examination. On Respiratory system examination, tactile vocal fremitus was increased in left infra scapular area. Also, fine Velcro crepts were heard bilaterally in Infra scapular area(ISA), Infra axillary area(IAA) and Inframammary area(IMA) with bronchophony in left ISA region on auscultation. Dull note over left IAA and ISA region was percussed. Laboratory examinations were as follows:

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Skin biopsy showed focal thinning of epidermis with subtle vacuolar changes and underlying dermis showed aggregates of lymphocytes, histiocytes and few plasma cells with areas of hemorrhage. T inversion in V1-V5, left axis deviation and sinus tachycardia was there on Electrocardiogram. Reticular opacities were noted in bilateral lower and left middle lung zones and radio opacity was noted in left lower lung zone on Chest X-Ray. HRCT Chest showed Diffuse ground glass opacities and consolidations in both lungs, predominantly left-sided, suggestive of infective/inflammatory cause. Additionally, small bilateral hilar and mediastinal lymph nodes noted, alongside dilated pulmonary arteries indicative of possible pulmonary arterial hypertension. On ANA and myositis profile, Ro-52 and MDA 5 were found to be strongly positive with fine speckled immunofluorescence and homogeneously positive cytoplasm giving the impression of Clinically Amyopathic Dermatomyositis with Rapidly progressive Interstitial Lung Disease in a case of Hypothyroidism.

Differential Diagnosis:

While the patient presented with skin conditions and positive ANA, similar to other autoimmune diseases, the absence of specific symptoms (like joint pain, dry mouth, etc.) and the presence of anti-MDA-5 antibodies strongly suggest a diagnosis of anti-MDA-5 positive amyopathic dermatomyositis.

Other potential diagnoses, such as SLE, Sjögren's Syndrome, and idiopathic interstitial pneumonia with autoimmune features (IPAF), were considered but ruled out due to the lack of specific symptoms or the presence of conflicting markers. Conditions like mixed connective tissue disease (MCTD), Systemic Sclerosis, and Paraneoplastic Dermatomyositis were also considered but were less likely given the patient's symptoms and test results.

Drug-induced myopathy and viral myositis were unlikely due to the absence of a relevant medication history and the chronic nature of the patient's symptoms. Psoriasis was also considered but was ruled out based on the lack of typical psoriatic features.

Considering the overall clinical picture and the presence of anti-MDA-5 antibodies, the most likely diagnosis is anti-MDA-5 positive amyopathic dermatomyositis, with a focus on early treatment due to the associated risk of rapid disease progression.

Treatment:

The patient was given Injection Ceftriaxone 1 gram intravenously 12 hourly, Tablet Thyroxine 50 microgram once a day before breakfast, Tablet Prednisolone 5 mg 6 tablets once a day with milk (dose increased from 4 to 6 tablets), Tablet Mycophenolate Mofetil 360 mg twice a day, Tablet Calcium 500 mg twice a day, Vitamin D3 sachet once a week and syrup Phenylephrine, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide (DMR) 2 tablespoon thrice a day. In view of rapidly progressive Interstitial Lung Disease, patient was started on Injection Rituximab one dose, Injection Cyclophosphamide 750 mg in 500 cc Normal Saline over 4-5 hours after 1 month followed by 2 doses of Inj. MESNA and Tablet of Tacrolimus 0.5 mg OD after 10 days. Despite intensive care, the patient succumbed to death.

Follow-up and outcome:

Patient was on weekly follow up till 1 month and then on biweekly follow for next 3 months. In between that patient deteriorated in the house and was not able to breath and had fainted and was brought to hospital where she was admitted to intensive care unit(ICU) and died one 4th day of his intensive care admission.

Discussion:

CADM(Clinically Amyopathic Dermatomyositis) primarily affects young adults, also cases of juvenile-onset have been reported in the literature.[10] Previous studies have shown that patients with dermatomyositis who are positive for anti-Tif1γ antibodies face a higher risk of cancer-related complications. Conversely, anti-MDA-5 antibodies have not been commonly linked to an elevated cancer risk.[8,11] The literature contains limited reports of cancer in patients with anti-MDA-5 antibody-positive rapidly progressive interstitial lung disease (RP-ILD) .[12, 13]

CADM primarily affects the skin but can also impact various organ systems like pulmonary -IDL(interstitial lung disease),rheumatology-Arthralgia ,myositis and Arthritis,GI-Dysphagia , Cardiac-cardiomyopathy etc. Muscle inflammation in myositis is associated with higher amounts of molecules mistaken by the body's defense system as harmful. This connection suggests a link between cancer and this muscle disease because these molecules are found in both cancerous and muscle tissues.The immune responses directed at tumors may also cause damage to muscle tissue in cases of dermatomyositis (DM) or polymyositis (PM).[14] Recent studies have revealed a paraneoplastic association between dermatomyositis (DM) and cancer, with approximately 24% of DM cases linked to malignancies. This relationship suggests an underlying immunological mechanism, characterized by distinct immunophenotypic patterns, including a predominance of CD4+ T cells and B cells in DM, coupled with a decrease in regulatory T cells. These findings indicate a maladaptive immune response to self-antigens and a possible interaction with antigens presented by cancer cells.[15] These observations have the important role of immune dysregulation in the etiology of DM and its significance as an indicator of concealed malignancies.

Interestingly, the patient initially presented with suspected psoriasis. Psoriatic lesions can resemble Gottron's papules, and therefore, especially in the absence of muscular symptoms, may be misdiagnosed.[16]

This case underscores the intricate interaction of various systemic and autoimmune disorders, culminating in a fatal outcome. The patient, a 60-year-old woman, presented with deep, painful skin ulcers and palmar papules, also known as inverse Gottron's papules, which are more

characteristic of anti-MDA-5 dermatomyositis (DM). Histological analysis of DM skin usually shows interface dermatitis. In the MDA-5 subtype, classic symptoms of dermatomyositis, including epidermal necrosis and vasculopathy, are observed, often accompanied by rapidly progressive interstitial lung disease (RP-ILD) and hypothyroidism.[17] The patient was administered a comprehensive treatment plan, which included antibiotics (Ceftriaxone) to address potential infections, immunosuppressive agents (Prednisolone, Mycophenolate Mofetil, Rituximab, Cyclophosphamide), and supportive therapies (Thyroxine, Calcium, Vitamin D3, and antitussive syrup). The intensification of immunosuppressive therapy, particularly with Rituximab and Cyclophosphamide, highlighted the critical and rapidly worsening condition of the ILD. For patients with resistant DM affecting the lungs and esophagus, intravenous immunoglobulin (IVIG) is crucial in treatment.[18] Studies have demonstrated that IVIG reduces complement activity, limits the deposition of the membrane attack complex on capillaries and muscle fibers, and decreases the expression of adhesion molecules and cytokine production. [9,19]

This case highlights the complex diagnostic and therapeutic challenges involved in managing such intricate presentations. Despite aggressive treatments, the patient's condition worsened, resulting in death.

“When a prevention campaign works, nothing happens!” ~Norman Swan
Thus, for patients with anti-MDA-5 antibody-positive CADM, early screening and consistent monitoring of complications are crucial to enhance morbidity outcomes and reduce mortality rates.

Key clinical message:

Anti-MDA-5 positive amyopathic dermatomyositis (CADM) can lead to rapid multisystemic complications, including severe interstitial lung disease (ILD). This case, involving a 60-year-old female with worsening skin lesions and ILD, demonstrates the disease’s aggressive nature, highlighting the need for early diagnosis and comprehensive immunosuppressive therapy to improve patient outcomes.

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Consent of patient:

We have taken written consent from patient regarding publishing clinical information as well as radiological image findings of patient, which would be open access and the patient is agreed with this condition.

Figure 1

Gottron’s rash - Plaques/Papules over MCP and PIP joints

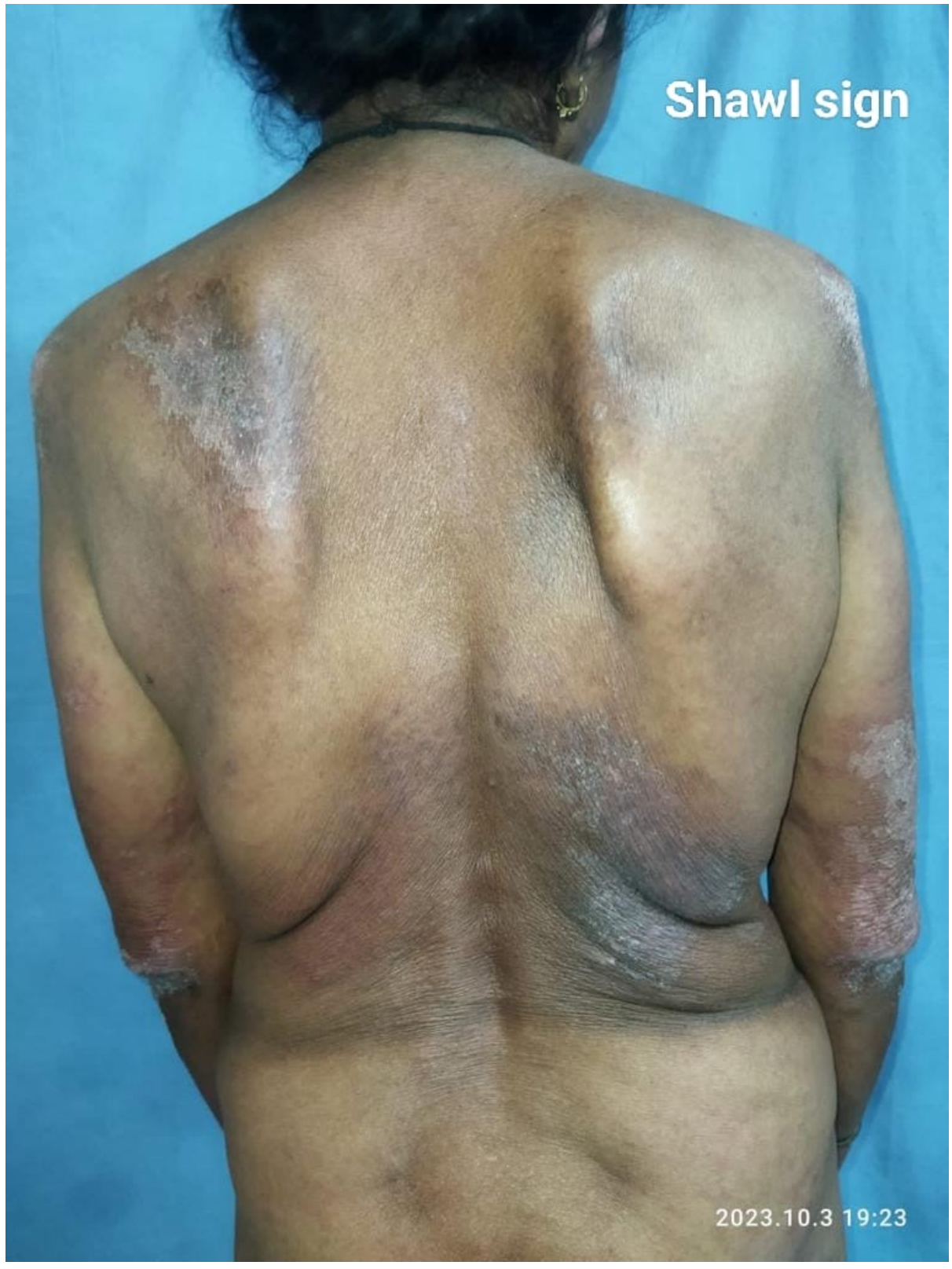

Figure 2

Shawl sign-Erythema involving back region

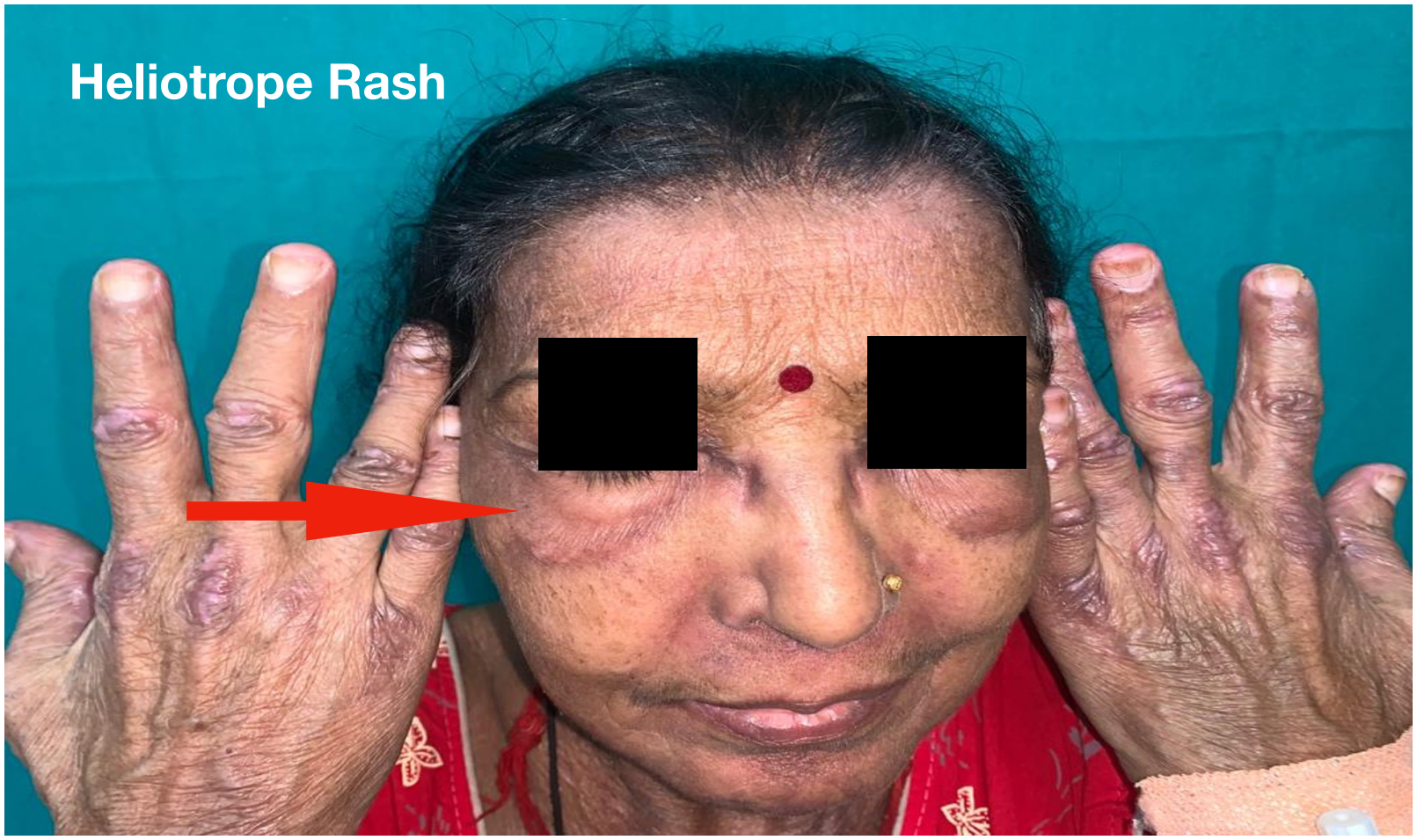

Figure 3

Heliotrope rash - Violaceous erythema involving periorbital region

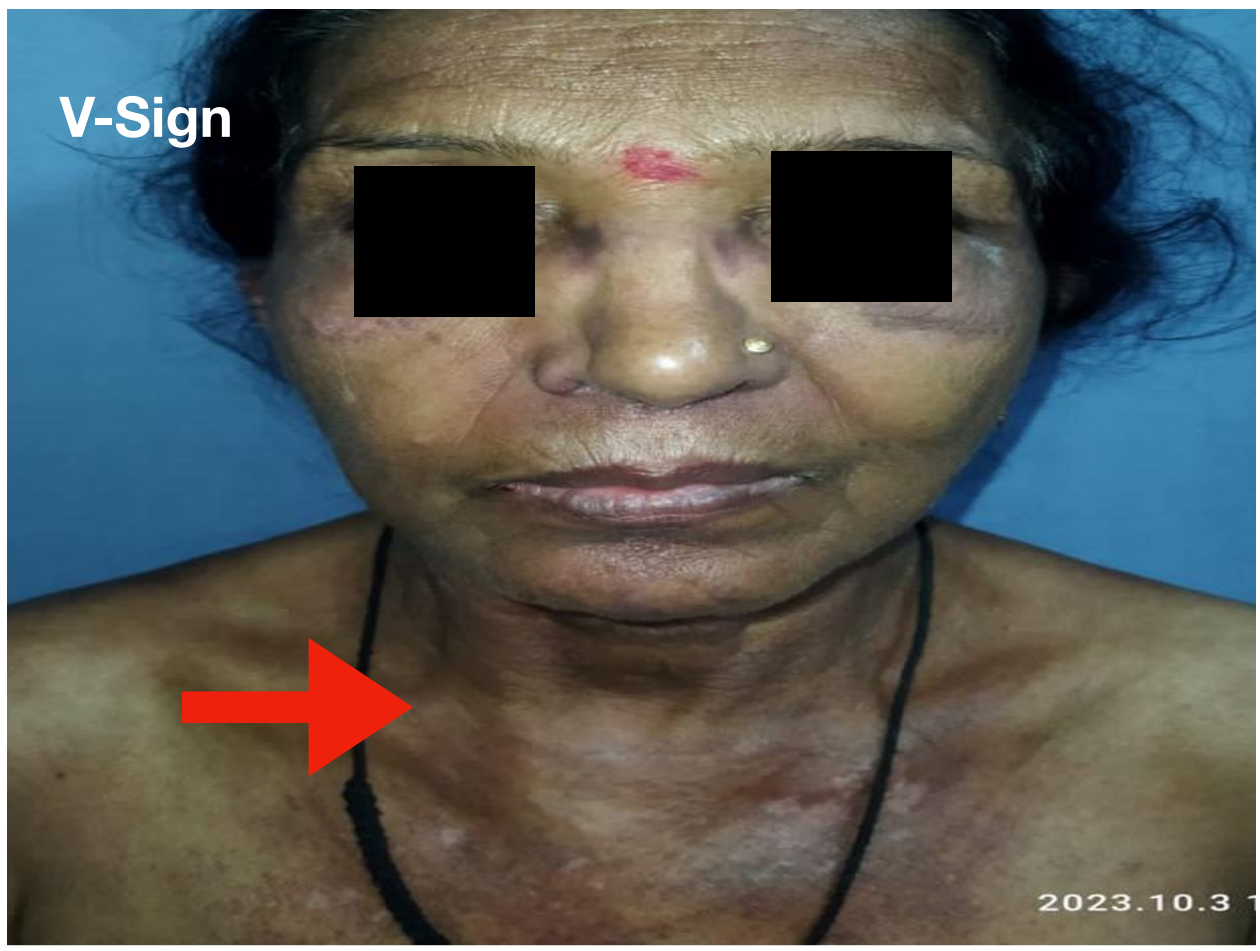

Figure 4

V-sign - Violaceous erythema involving front of neck

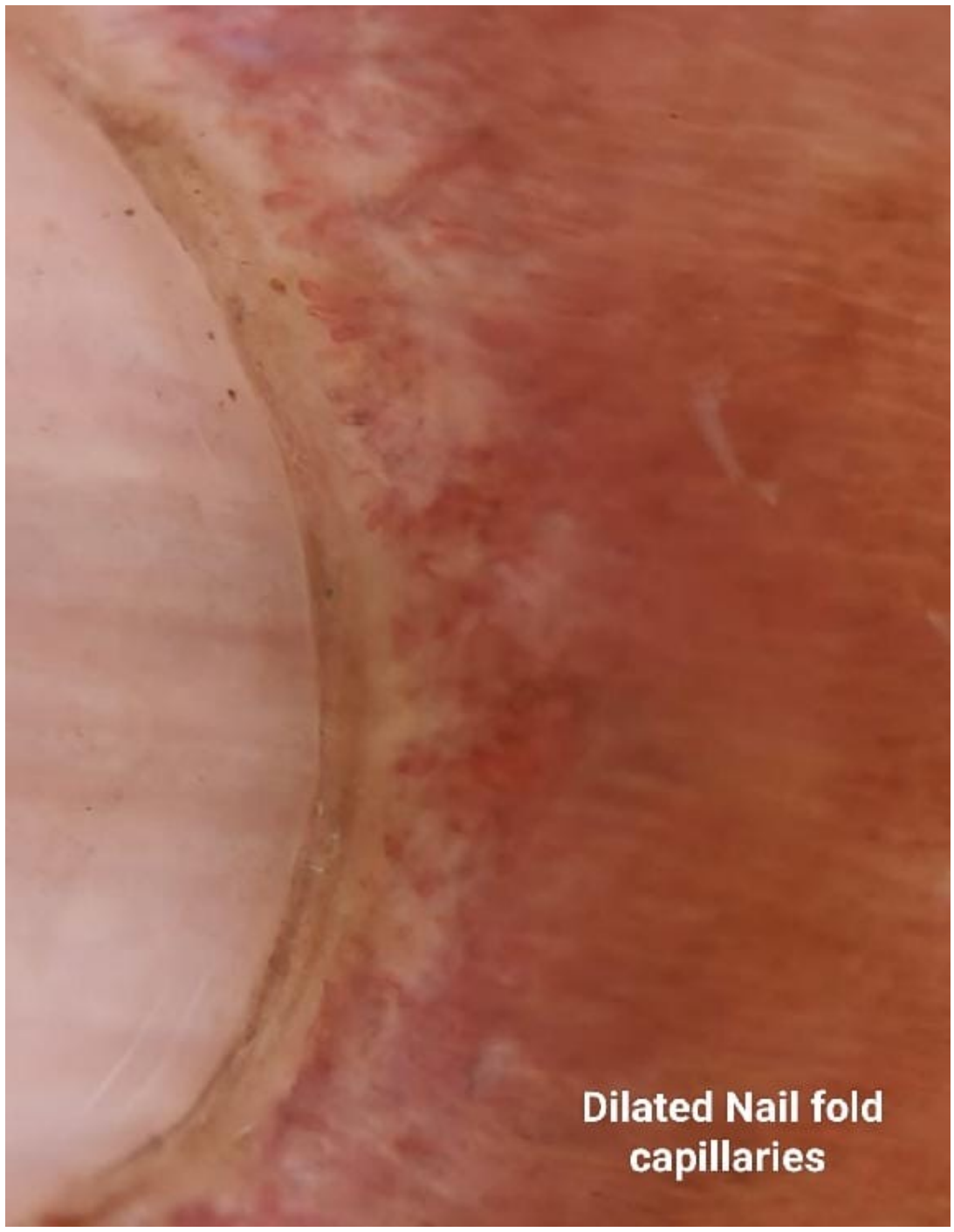

Figure 5

Nail fold telangiectasia-Dilated nail fold capillaries

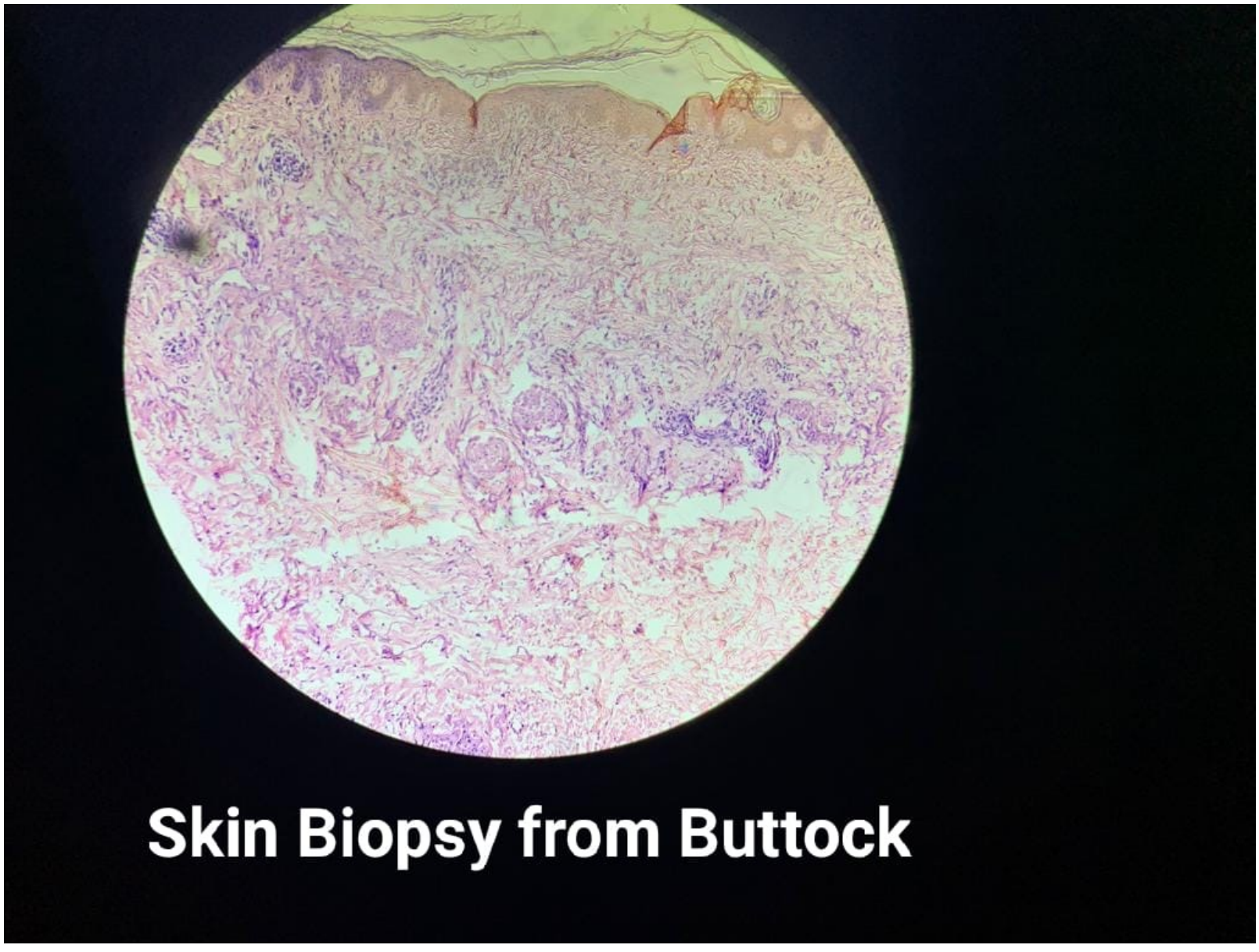

Figure 6

Skin Biopsy

Shows focal thinning of epidermis with subtle vacuolar changes.

Underlying dermis shows aggregates of lymphocytes, histiocytes and few plasma cells with areas of haemorrhage.

S/O - DERMATOMYOSITIS

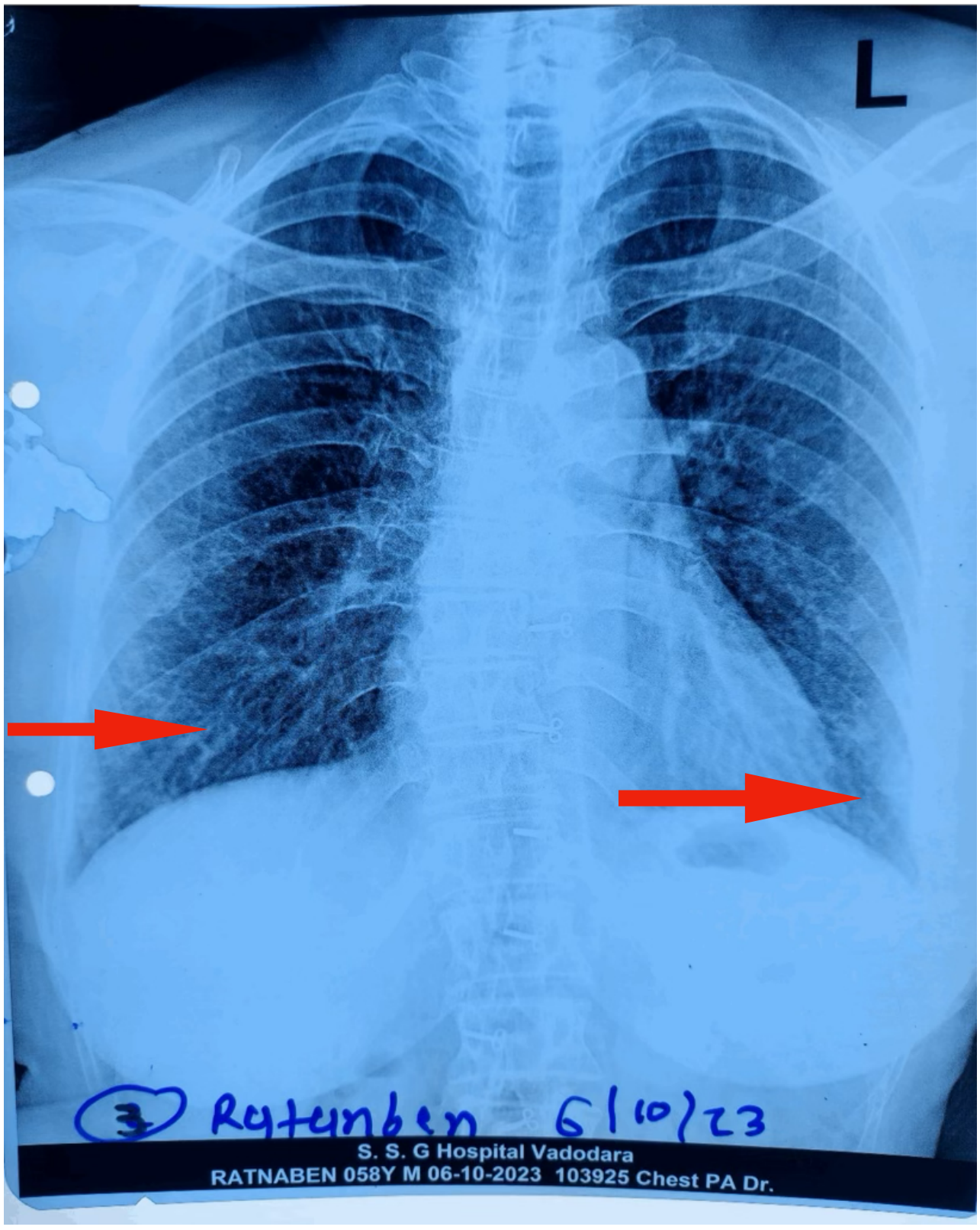

Figure 7

Reticular opacities noted in B/L lower and left middle lung zones

d

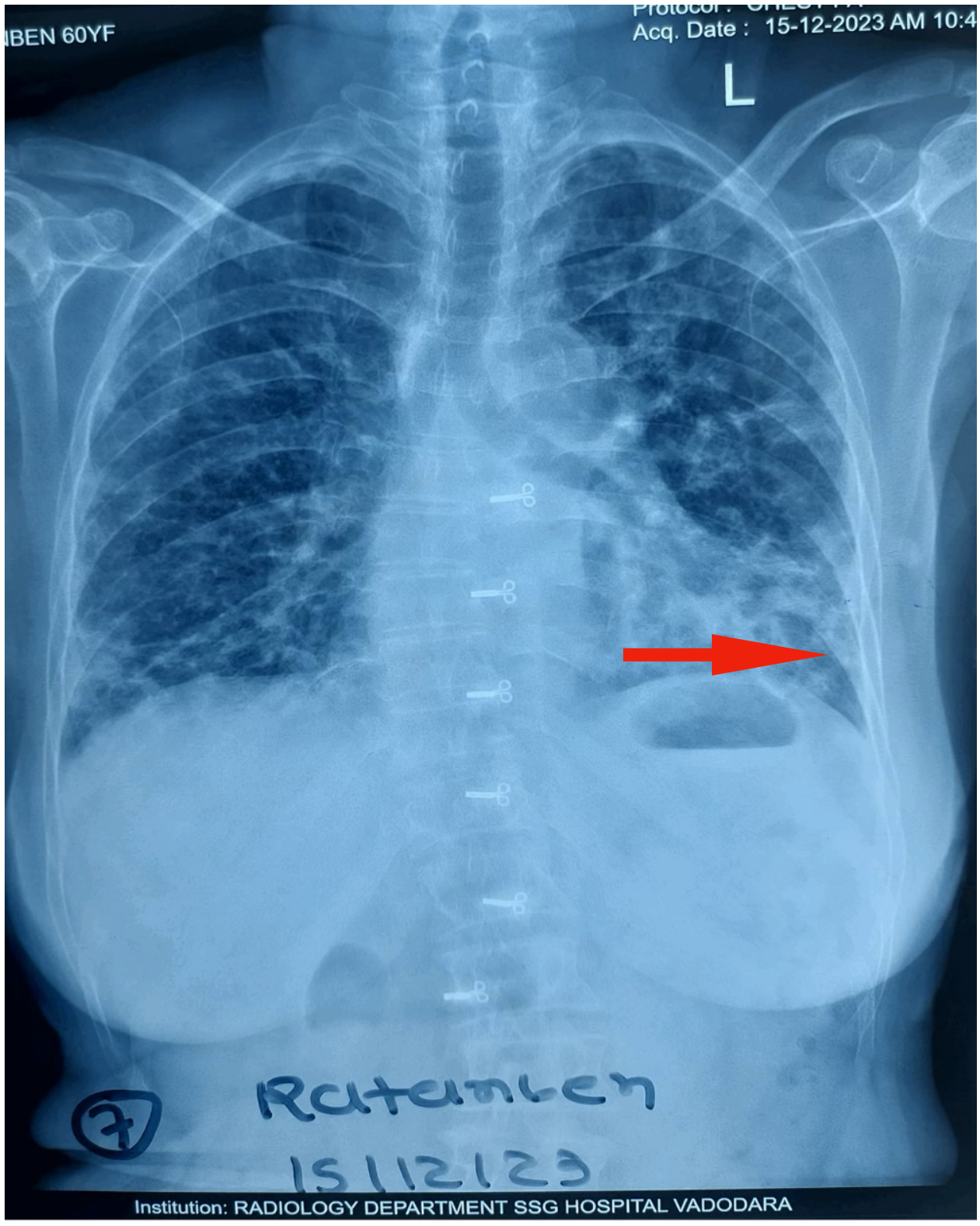

Figure 8

Radio-opacity noted in left lower lung zone-

p/o consolidation

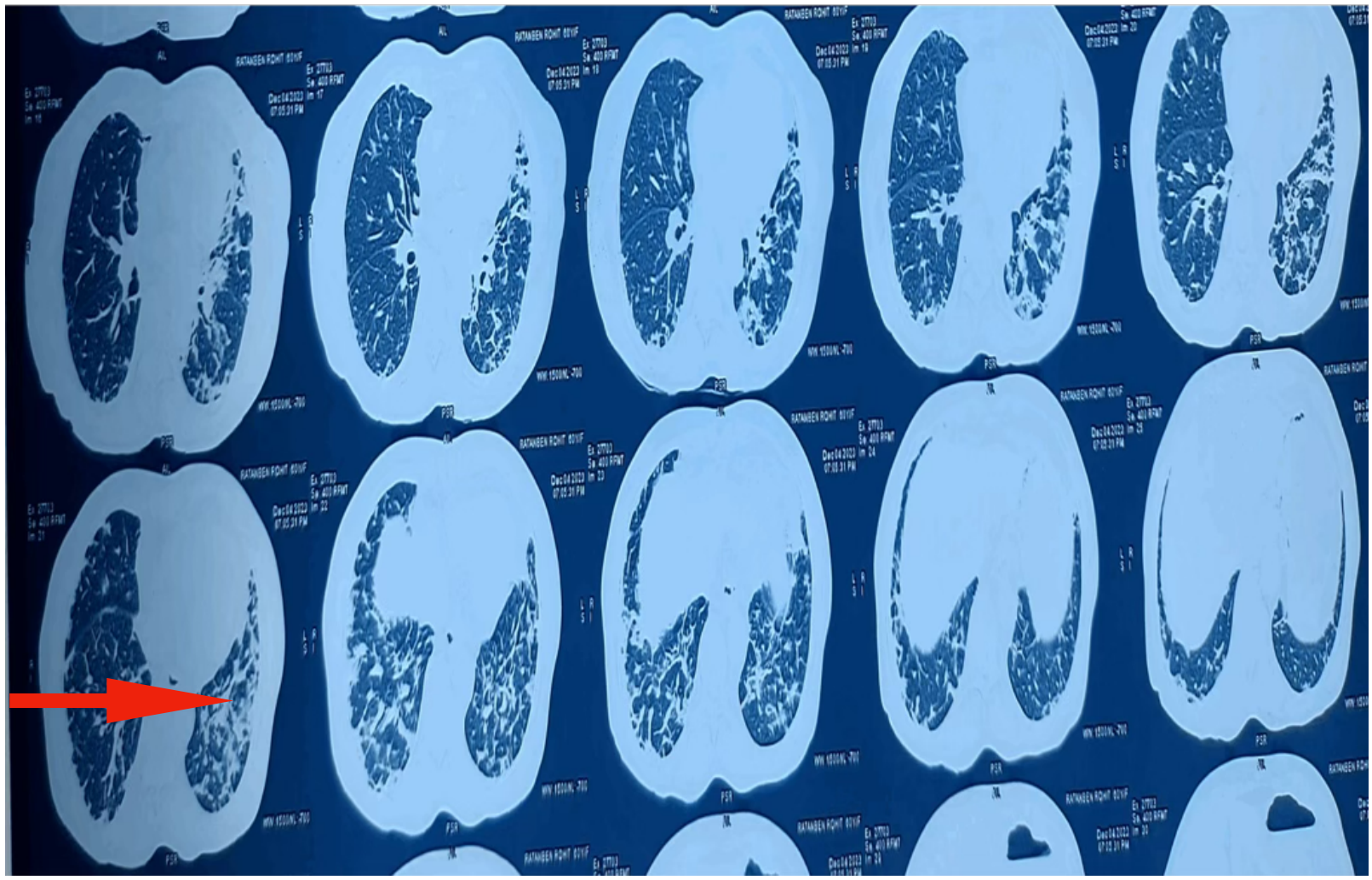

Figure 9

HRCT CHEST

Multifocal diffusely scattered ground glass and reticular densities and consolidation in both the lungs predominantly on left side represent infective/ inflammatory etiology.

Few subcentimeter size bilateral hilar, pre and paratracheal, paraaortic, aorto-pulmonary window and subcarinal lymphnodes.

Dilated right and left pulmonary arteries may represent pulmonary arterial hypertension