Clinical Spectrum of Connective Tissue Disorders

Mohammad Bagher Owlia*

Introduction

Rheumatology is one of the new branches of internal medicine which appears to have been around for not more than 55 - 60 years1. The 1990s were a time of new awareness of the subtleties of rheumatic diseases and how, with closed inspection, different syndromes could be separated out from what seemed initially to be the same basic disease. So the classification of the inflammatory rheumatic disorders is quite challenging2.

Many specific conditions manifest principally in the musculoskeletal system, such as connective tissue diseases, inflammatory arthritis, osteoarthritis and osteoporosis3. The economic burden of rheumatic diseases is often more substantial than other chronic conditions, including cardiovascular diseases and cancer4. Unfortunately, arthritis and rheumatic diseases receive far less attention in the scientific literature than is warranted by their enormous and growing disease burden5. Eliciting and interpreting clinical signs is essential in diagnosing many rheumatic disorders, but the sensitivity and specificity of many of these signs for any given disorder remains poorly categorised6. On the other hand it seems that clinical rheumatologic expertise among general practitioners is low in most centres; for example, in one study, a lack of correlation between clinical manifestations and subsequently requested laboratory examinations was found in the referral letters by general practitioners (GPs), exemplified by the use of HLA-B27 in rheumatoid arthritis and serum rheumatoid factor in ankylosing spondylitis. These results showed that among GPs, the threshold for referring patients to a rheumatology outpatient clinic appears rather high, and that patients are subjected to long observation periods before referral7, 8. Subsequently, they are poorly managed because of lack of priority and inadequate competencies due to limited medical education in this spectrum of conditions9.

Many authors believe that nearly all cases of connective tissue disorders need rheumatology visit within six weeks of onset of symptoms because early, aggressive treatment is essential to achieve the best outcome in patients with inflammatory arthritis10.

Rheumatology by itself is divided generally into two parts: Immune mediated and non-immune mediated disorders. The collagen and connective tissue is the main target for most immunological reactions. So you can imagine the diversity of clinical spectrum of connective tissue diseases (CTDs) as the reflection of dispersion of collagen in the human body, i.e., the whole body.

According to MESH system of national library of medicine, the term “connective tissue disease” (CTD) (Year introduced: 1980) is defined as a heterogeneous group of disorders, some hereditary, others acquired, characterised by abnormal structure or function of one or more of the elements of connective tissue, i.e., collagen, elastin, (and cells) or the mucopolysaccharides. But most clinicians limit this term to a group of autoimmune disorders that are classified among the systemic rheumatic diseases and include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis-dermatomyositis (PM-DM), primary Sjögren’s syndrome (SS), primary antiphospholipid syndrome (APS), and mixed connective tissue disease (MCTD)11. Since most of CTD-specific features are neither frequent nor pathognomonic for an individual disease, the most common way to identify CTD is considering a combination of clinical and laboratory findings. This is also the major reason why classification criteria have been developed for CTDs. CTDs share a number of epidemiological and immunological features that suggest a common pathogenetic mechanism. The sharing of immunogenetic features may, to some extent, lead to the development of common clinical features. Among these, the most frequent are arthralgia/arthritis and Raynaud’s phenomenon, often associated with antinuclear antibodies12 and/or rheumatoid factor; taken together, these

* Assistant Professor and Head, Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
features constitute a clinical syndrome that can often represent the onset of a CTD.

Herein the author has attempted to present an overview on clinical spectrum of connective tissue diseases not only for students in medicine, but also for practicing physicians in internal medicine and rheumatology field.

Constitutional symptoms

Most of CTDs may present with systemic signs of inflammation such as fever, weight loss, anorexia and malaise, vague generalised pain or fatigue which also may mimic other non-collagen vascular diseases like fibromyalgia or chronic fatigue syndrome. The autoimmune disorders like SLE and adult-onset Still's disease are among the differential diagnoses of fever of unknown origin (FUO). Fever occurs frequently in several rheumatic disorders, and remains a diagnostic and therapeutic challenge to the rheumatologist in spite of the great advances made in the fields of medical diagnosis and technology. It could be the initial symptom of a rheumatic disease, but it could also be the expression of a disease flare, of an infectious complication, of a secondary neoplasm, or be of iatrogenic origin. The pathogenesis of fever in rheumatic diseases is still quite unclear; however, recently IL-1, IL-6 and other endogenous pyrogens, such as tumour necrosis factor (TNF-\(\alpha\)) , have been shown to play a pivotal role in causing pyrexia during inflammatory conditions. Fever is not a striking feature of SSc, and APS due to non-inflammatory nature of this syndromes unless it is be complicated with other conditions. Although the Raynaud’s phenomenon, puffy hands and arthralgia are the most common presentations in MCTD, occasionally high fever alongwith signs of muscle pain and weakness may be seen at first presentation.

Musculoskeletal

Arthritis is one of the most prevalent chronic conditions among adults in the United States affecting more than 15 - 16% of the population overall, and more than 20% of the adult population.

Inflammation of the joint, i.e., arthritis is a term that is used to describe more than hundred different rheumatic diseases. It is the leading cause of disability. Although arthritis affects 50% of individuals older than 65 years, most people with arthritis are younger than 65 years and still of working age. Why joints are frequently involved in CTDs? We know that interior surface of all diarthrodial joints are lined with a layer (synovia) which is composed of potentially active cells. Synovioyte A and B act as tissue macrophage and fibroblast respectively which are among the most important cells that may contribute to immunologic processes.

Articular manifestations of CTD range from simple inflammatory arthralgia to overwhelming acute arthritis. Around 10% of peoples with rheumatoid arthritis (RA) present initially with severe arthritis in association with fever and other systemic manifestations. Patterns of additive individual joint involvement are diagnostic for RA. Erode and deforming nature of arthritis distinguishes it from most of other articular involvement in CTDs. Monarthritis which itself may bring in the mind the concept of septic or crystal arthropathies may be the single initial feature of a known systemic condition such as RA. But in general term, joint problems in many CTDs is in the form of peripheral symmetric arthritis involving more commonly the small joints. Prevalence of arthralgia or arthritis in RA is about 100%, in SLE, 95%, MCTD (90%), SSc (40 - 70%), Primary SS (60%), PM-DM ( 35 - 50% ), and in APS (27 - 39%).

Other manifestations of this category include myalgia, myopathy, myositis (DM-PM, SSc, SLE, and MCTD), avascular necrosis (SLE), and osteoporosis of bones (RA). Soft tissue rheumatism or inflammation of periarticular structures such as bursa, tendons or tenosynovium and planter fascia (inflammatory heel pain) may precede months-to-years before evolution to a full picture of rheumatoid arthritis.

Mucocutaneous

Skin manifestations of CTDs are very diverse and protean. This organ is involved in all cases of Dermatomyositis (Gottron sign, Heliotropic rash, Mechanic’s hand, Shawl and V sign) and SSc (scleroderma, telangiectasia, hypo and hyperpigmentation) and about 80% in SLE (photosensitivity, malar rash, alopecia). Many cutaneous features of CTD are subtle and not disturbing for patient. The author had many CTDs presenting with minimal skin changes. Apart from periungual erythema, painful erythematosus lesions of extremities frequently heralded the vasculitis secondary to CTD evolving to periungual infarcts. Janeway lesions and Osler’s nodes may be seen in severe life-threatening flares.
of lupus\textsuperscript{19}. Raynaud’s phenomenon\textsuperscript{20} which is a vasospastic condition provoked by cold, emotional stressors, and vibration is found in more than 90% of SSc and some other CTDs including SS (37%). First step in approaching patients with Raynaud’s phenomenon is to examine nail folds looking for capillary changes which strongly suggest secondary causes of RP. Less than 50% of patients with RP attending a rheumatology specialty centre have a connective tissue disease\textsuperscript{21}.

Livedo reticularis is the cutaneous hallmark of APS (11 - 24%) as well as SLE\textsuperscript{22}. Rheumatoid nodule is said to be found in 20 - 30% of RA patients but it seems to be less frequent in our practice. Leukocytoclastic vasculitis is the commonest vasculitic lesions in RA patients. Palmar erythema and pyoderma gangrenosum are seen in RA as well\textsuperscript{23}.

Alopecia and/or hair thinning, especially when it is associated with inflammatory changes of the scalp, are a sign of lupus. Bullous and urticarial lesions may be a clinical dilemma in some cases of SLE. Bullous lupus erythematosus (BSLE) is a rare subset of systemic lupus erythematosus (SLE), often associated with autoimmunity to type VII collagen\textsuperscript{24}. Photosensitivity and malar rash are present in 70% and 50% of SLE patients respectively. Polycyclic lesions with central sparing are seen in subacute cutaneous lupus (SCLE). Lichen planus-like lesions and panniculitis (lupus profundus) may be seen rarely in SLE. Of these, the most strongly associated with SLE is malar rash\textsuperscript{25}. Painless oral lesions (40%) are a frequently ignored positive finding in physical examination. Although dry mucosa (Sicca syndrome) is the outstanding feature of Sjögren syndrome, Raynaud’s phenomenon and vasculitic lesions including purpura and recurrent urticaria may also occur\textsuperscript{18}.

Splinter haemorrhage and skin necrosis are also seen in APS\textsuperscript{18, 26}. Rheumatologic skin manifestations such as dermatomyositis/polymyositis, and paraneoplastic vasculitis are the most frequently recognised paraneoplastic syndromes. Other less known associations are fasciitis, panniculitis, erythema nodosum, Raynaud’s syndrome, digital gangrene, erythromelalgia and lupus like syndromes\textsuperscript{27}.

Cardiovascular

First descriptions about cardiovascular manifestations (mostly myocarditis and endocarditis) in inflammatory rheumatic diseases are dated at the end of the 19th century. Inflammatory rheumatic diseases show an increased cardiovascular morbidity and mortality\textsuperscript{28}.

Cardiovascular involvement is more prominent in SLE (60% of cases) in the form of pericarditis, myocarditis, myocardial infarction, endocarditis (Libman-Sacks) and interstitial fibrosis of the heart. Atherosclerosis occurs prematurely in patients with systemic lupus erythematosus and is independent of traditional risk factors for cardiovascular disease\textsuperscript{13, 29}. But clinically apparent heart disease in RA is really rare including asymptomatic pericarditis in upto 50% of cases. Constrictive pericarditis may occur very rarely.

Cardiac involvement in SSc occurs in about 10% of cases and consists of degeneration of myocardial fibres and some interstitial fibrosis. Fibrosis may cause damage to conductive system leading to atrio-ventricular conduction defect. Pericarditis and effusion may occur. Raynaud’s phenomenon is a vascular condition involving the distal vessels of extremities. Cardiovascular involvement is more prominent in SLE (60% of cases) in the form of pericarditis, myocarditis, myocardial infarction, endocarditis (Libman-Sacks) and interstitial fibrosis of the heart. Atherosclerosis occurs prematurely in patients with systemic lupus erythematosus and is independent of traditional risk factors for cardiovascular disease\textsuperscript{13, 29}. But clinically apparent heart disease in RA is really rare including asymptomatic pericarditis in upto 50% of cases. Constrictive pericarditis may occur very rarely.

Cardiac involvement in SSc occurs in about 10% of cases and consists of degeneration of myocardial fibres and some interstitial fibrosis. Fibrosis may cause damage to conductive system leading to atrio-ventricular conduction defect. Pericarditis and effusion may occur. Raynaud’s phenomenon is a vascular condition involving the distal vessels of extremities. Cardiovascular involvement is more prominent in SLE (60% of cases) in the form of pericarditis, myocarditis, myocardial infarction, endocarditis (Libman-Sacks) and interstitial fibrosis of the heart. Atherosclerosis occurs prematurely in patients with systemic lupus erythematosus and is independent of traditional risk factors for cardiovascular disease\textsuperscript{13, 29}. But clinically apparent heart disease in RA is really rare including asymptomatic pericarditis in upto 50% of cases. Constrictive pericarditis may occur very rarely.

APS has several cardiovascular features similar to SLE such as valvular abnormality (upto 63%), thickening (11.6 %), vegetations (2.7 - 4%), myocardial infarction (5.5%), and intracardiac thrombi and coronary bypass re-thrombosis\textsuperscript{15, 30}.

Arterial and venous thrombosis is typical for primary or secondary APS (around 60%), and SLE (15%). Acute involvement at the level of capillaries, arterioles, or venules often results in clinical picture really indistinguishable from those of haemolytic-uraemic syndrome and TTP. Arterial thromboses are less common than venous thromboses and the brain is the most common site in this regard. It occurs in almost 50% of arterial occlusions followed by coronary occlusions in additional 23\textsuperscript{28}. Overwhelming extensive vascular thrombosis and resultant multiple organ involvement is a dreaded complication in catastrophic APS\textsuperscript{31}. Hypertension is a rule in APS when renal artery is involved\textsuperscript{32}. In every case of pulmonary embolism on the basis of SLE, secondary APS must be strongly considered. Amaurosis fugax (2.8%) may be the first presentation of APS secondary to vascular insult in retinal vessels\textsuperscript{33}. 

Journal, Indian Academy of Clinical Medicine • Vol. 7, No. 3 • July-September, 2006 219
Lymphoedema is a somewhat rare complication of RA that may be secondary to lymphangitis in the context of inflammatory polyarthritis. The diagnosis of rheumatoid lymphoedema is clinical – based on painful swelling of a whole limb in association with RA – and it does not appear to be correlated with positivity for rheumatoid factor, nor with the clinical activity of the disease. Cardiac involvement in primary SS is notably unusual.

**Pulmonary**

Lungs are frequently involved in the process of autoimmune disorders. Pleurisy (50%), pleural effusion (30%), and interstitial fibrosis have indolent course in some cases of SLE, but lupus pneumonitis (10%) and diffuse alveolar hemorrhage (2-5%) have a more serious course, and the later may be the first manifestation of SLE and has very high mortality rate. Pulmonary hypertension in isolated form or secondary to APS may occur (<5%). Males more often show pleuritis as a first symptom. Lung involvement in MCTD is usually asymptomatic but occurs in 85% of patients in the form of decreased capacity of lungs for diffusion of carbon monoxide (DLco). Pulmonary hypertension is the leading cause of mortality in MCTD.

Pulmonary involvement occurs in at least two-thirds of SSc patients, and now is the leading cause of death replacing renal failure. The most frequent complaint is exertional dyspnoea and often with non-productive cough. Pulmonary function test usually disclose low diffusing capacity and low PO2 during exercise. Both interstitial fibrosis and vascular lesions may occur. Acute alveolitis, which is really an emergency situation, may occur and appear as ground-glass appearance on high resolution CT scanning (HRCT). Fewer than 10% of patients will develop pulmonary arterial hypertension with very poor prognostic index (with only 2 years survival in most).

Pleuropulmonary manifestation of RA include asymptomatic pleural effusion and pleuritis, interstitial fibrosis – which is more common in male patients, pleuropulmonary nodule, pneumonitis, and arteritis.

Rheumatoid nodules may mimic vasculitic lesions of Wegener's granulomatosis or neoplastic infiltration. Bronchopleural fistula and pulmonary hypertension are complications of cavitated nodules and obliteration of pulmonary vasculature respectively. Incidence of airway hyper-reactivity in RA cases is higher in cigarette smokers. Eosinophilic pneumonia is reported by Norman as an initial presentation of RA.

Pulmonary embolism may occur in 14% of APS cases. Other rare manifestations of APS are pulmonary hypertension, microthrombosis, fibrosing alveolitis, pulmonary artery thrombosis, and diffuse alveolar hemorrhage.

In PM-DM, lungs are involved in the form of respiratory insufficiency due to respiratory muscle weakness and interstitial lung disease but it occurs infrequently.

Dry throat and trachea (xerotrachea) is the pulmonary manifestation of SS.

**Neuropsychic**

SLE and APS are the most frequent CTDs presenting with neurologic and psychiatric manifestations. Migraine (20%), stroke (19.8%), transient ischaemic attack, epilepsy, multi-infarct dementia, transient amnesia, cerebral venous thrombosis, and ataxia as well as transverse myelopathy and multiple sclerosis-like lesions are among the most frequent features in APS.

Neurologic manifestations occur in 60% of SLE patients. The cognitive dysfunction (including deficit in intelligence, attention, reasoning, learning, recall, fluency, language, and perceptual motor capacity), and headache are among the most frequent features of neuro-psychiatric lupus (NPSLE). The term organic brain syndromes is no longer recommended for use. Psychosis (10%), and seizures (20%) are the most important issues incorporated in classification criteria of SLE. Peripheral neuropathies, extrapyramidal, cerebellar dysfunction, subarachnoid haemorrhage, transverse myelitis (in association with APS in nearly all cases), and syndrome of inappropriate ADH secretion (SIADH) are relatively rare. Other rare NPSLE manifestations are myasthenia gravis (MG), Guillain-Barre syndrome. Transverse myelitis, optic neuropathy, and epilepsy are associated with APS, suggesting a role for early anticoagulation when these entities are encountered.

Electroencephalography (EEG) is abnormal in up to 70% of SLE patients.
RA tends to spare the central nervous system directly but peripheral nerves may be damaged in the context of rheumatoid vasculitis. Central nervous system involvement in rheumatoid arthritis can rarely occur in the absence of systemic disease. Rheumatoid meningitis has been reported in 2005 by Chowdhry et al. Pure sensory peripheral polyneuropathy is a relatively common phenomenon in RA. Mononeuritis multiplex is a typical presentation of vasculitis secondary to RA or other CTDs. Cervical myelopathy is a morbid sequel of long-lasting seropositive RA. Bilateral carpal tunnel syndrome may occur as a result of proliferating synovitis of wrists compromising the median nerve. Sensori-neural hearing loss was found in about 50% patients with Sjögren syndrome which is correlated to the presence of anticycardiolipin antibodies. Primary SS with vasculitis may also present with multi-focal, recurrent, progressive nervous system disease such as hemiparesis, peripheral neuropathy, transverse myelopathy, aseptic meningitis, seizures, and movement disorders. Multiple sclerosis has also been reported in these cases. Trigeminal neuralgia is a classic manifestation of nervous system in SSc and mixed connective tissue diseases (MCTD). Renal crisis in SSc is characterised by malignant hypertension, which can progress rapidly to hypertensive encephalopathy, severe headache, retinopathy, and seizures. Male impotence in SSc may be as a result of autonomic nervous system dysfunction.

**Haematologic**

Haematologic manifestations may occur in 85% of SLE patients, of which the ‘anaemia of chronic disease’ is the most frequent one (70%). Leukopenia has usually a benign course and is four times as frequent as thrombocytopenia in SLE. Lymphadenopathy and splenomegaly is not uncommon in these patients (15%). Coomb’s-positive haemolytic anaemia and thrombocytopenia are common features of SLE and APS. Thrombocytopenia below 30,000 in SLE may be an indicator of association with APS and thromboembolic disease. Anaemia of chronic disease is common in long-lasting RA. Felt’s syndrome comprises of chronic RA, neutropenia and splenomegaly. Neutropenia is seen frequently in RA apart from Felt’s syndrome. Eosinophilia may be an indicator of severe disease, on the other hand benign eosinophilia may be under estimated in RA due to corticosteroid therapy. RA is associated with an increased incidence of large B cell lymphoma. Lymphadenopathy (14%), splenomegaly, and frank lymphoma (6%) are the haematologic features of Sjögren’s syndrome. Microangiopathic haemolytic anaemia is a typical haematologic manifestation of SSc in the presence of scleroderma renal crisis.

**Gastrointestinal**

Nausea — sometimes with vomiting and diarrhoea — and acute abdominal pain secondary to peritonitis can be manifestations of SLE flare. The most dreaded complication of intestinal lupus is vascular events including vasculitis and vascular thrombosis as a result of APS. The majority of SSc patients suffer from gastrointestinal involvement. The symptoms include epigastric burning pain, reflux oesophagitis, retrosternal pain, Barret’s oesophagitis, dysphagia, gastrointestinal hypomobility (and resultant bloating), early satiety, and pseudo-obstruction. Bacterial over-growth may result in malabsorption syndrome.

Oesophageal mucosal atrophy, atrophic gastritis, and subclinical pancreatitis are gastrointestinal features of SS. Oesophageal dysmotility is seen in 70% of MCTD patients.

Sometimes APS may manifest in gastrointestinal tract as splenic and pancreatic infarction (0.5 - 1%).

**Nephrologic**

Kidneys are among the most vulnerable organs in systemic autoimmune disorders. It is in part due to the huge capillary bed and negatively charged basement membrane. Apart from microscopic changes in connective tissue diseases, hypertension, haematuria, proteinuria, pyuria and urinary sediment changes are common clinical problems in these conditions. SLE is the prototypic condition in this regard. Kidneys are not frequently involved in RA except for amyloidosis as a long term complication of chronic inflammatory disease and reflection of drug effects commonly used in RA.

Renal disease occurs in about 2.7% of APS patients in the form of glomerular thrombosis, renal infarction, renal artery
and venous thrombosis.

Renal diseases occur more frequently in diffuse form of SSc. Malignant hypertension, haematuria, proteinuria, and frank renal failure are the manifestations. The presence of a large pericardial effusion may herald subsequent renal failure. The most frequent renal involvement in MCTD is membranous glomerulonephritis which occurs in 25% of patients.

Miscellaneous

**Endocrinologic:** Hypothyroidism occurs in substantial number of patients with SSc and Sjögren’s syndrome and may be associated with high anti-thyroid antibody titres. On the other hand, hypothyroidism may mimic many rheumatologic conditions such as RA. Generally autoimmune thyroid diseases occur more frequently in CTDs notably RA and SLE. High levels of muscle enzymes are seen in both idiopathic inflammatory myopathies and hypothyroidism.

**Obstetric:** Fertility rate is normal in SLE, but prematurity and stillbirth is more common than control group. More obstetrical features happen in the context of APS, so that foetal loss below 10 weeks occurs in about 35%, and late foetal losses (more than 10 weeks) in 17%.

**Ophthalmic:** Is more prominent in Sjögren’s syndrome (majority of patients), SSc and RA in up to 20% of cases in the form of sicca syndrome. Episcleritis and scleritis occur in less than 1% of RA patients. In SLE, sicca syndrome (15-30%) episcleritis, conjunctivitis, retinal vasculitis (5%) have been reported. Amaurosis fugax and sudden painless visual loss secondary to retinal vessel thrombosis is typical for APS.

**Undifferentiated connective tissue diseases:** These are a group of CTDs which may present with nonspecific symptoms and signs of autoimmune disorders for months or even years before they can be classified into a known rheumatologic classification.

Some parasitic infestations and chronic infections such as leprosy may underlie the clinical presentation of some rheumatic conditions. Given the continued and growing number of patients at risk for infections and infestation by virtue of their country of origin, travel habits, and an immunocompromised state, potential infections and infestations must be considered in patients undergoing evaluation for rheumatic complaints.

**Conclusion**

Extremely diverse clinical spectrum of connective tissue disorders merits more attention and caution in caring for patients with musculoskeletal problems. Really any organ may be involved by collagen vascular diseases, so we may consider rheumatology among the broadest fields in clinical practice. The author has tried to present an overview of these protein presentations in such conditions. Malpractices among non-experts in the field of rheumatology make our responsibility more difficult in training the under-graduate and post-graduate students.

**Acknowledgement**

I would like to express my appreciation for my dear colleagues Dr Hossein Soleimani, Dr Anousheh Haghighi, rheumatologists, and Dr Mozaffari, nutritionist, for their useful comments.

**References**

10. Clemens LE. The role of the rheumatologist in managing

ANNOUNCEMENT

4th National Conference of Cardiology, Diabetology, Electrocardiology and Echocardiography
18th & 19th November, 2006

Venue
Hotel Jehan Numa Palace, Bhopal (M.P.)

Registration Fees in Indian Rupees

<table>
<thead>
<tr>
<th>Category</th>
<th>Upto 30.07.06</th>
<th>01.08.06 to 30.09.06</th>
<th>01.10.06 to 10.11.06</th>
<th>Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Accommodation</td>
<td>1,200</td>
<td>1,500</td>
<td>2,000</td>
<td>2,200</td>
</tr>
<tr>
<td>*With Accommodation</td>
<td>2,500</td>
<td>3,000</td>
<td>3,500</td>
<td>4,500</td>
</tr>
<tr>
<td>Echo workshop</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
</tr>
</tbody>
</table>

* Accommodation will be provided on twin sharing basis.

Bank Draft drawn in favour of ICC-CON should be sent to the address mentioned below:

Conference Secretariat
Dr. P.C. Manoria
E-5/103, Arera Colony, Bhopal, M.P. - 462 016
Phone: 0755-2422299, Mobile: 9893042229
Fax: 0755-2532405, E-mail: pmanoria@rediffmail.com