A STUDY ON CUTANEOUS ADVERSE DRUG REACTIONS TO IMATINIB

Dissertation submitted in partial

fulfillment of university regulations for

M.D. DEGREE in

DERMATOLOGY, VENEREOLOGY & LEPROSY

BRANCH XX

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled **"A STUDY ON CUTANEOUS ADVERSE DRUG REACTIONS TO IMATINIB"** submitted by **Dr.S.SARANYA** to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfilment of the requirement for the award of M.D. [DERMATOLOGY, VENEREOLOGY AND LEPROSY] and is a bonafide research work carried out by her under direct supervision and guidance. This work has not previously formed the basis for the award of any degree or diploma.

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DECLARATION

I**, Dr.S.SARANYA**, solemnly declare that the dissertation titled **'A STUDY ON CUTANEOUS ADVERSE DRUG REACTIONS TO IMATINIB'** is a bonafide work done by me at Government Rajaji Hospital during 2017 – 2020 under the guidance and supervision of **Prof.Dr.G.GEETHARANI M.D., DD**., Professor and Head of the Department of Dermatology, Madurai Medical College, Madurai. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree and diploma to any university, board either in India or abroad. The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, towards partial fulfilment of requirement for the award of M.D. Degree in Dermatology, Venereology and Leprosy (BRANCH –XX).

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CONTENTS

ANNEXURES

ABBREVIATIONS

CADRs	- Cutaneous Adverse Reactions
TKs	- Tyrosine Kinases
CML	- Chronic Myeloid Leukemia
GIST	- Gastrointestinal tumour
NEH	- Neutrophilic Eccrine Hidradenitis
DRESS	- Drug Related Eosinophilia And Systemic Syndrome
TEN	- Toxic epidermal necrolysis
SJS	- Stevens Johnson syndrome
AGEP	- Acute generalized exanthematous pustulosis
PRP	- Pityriasis rubra pilaris
PDGR	- Platelet-derived growth factor receptor

INTRODUCTION

INTRODUCTION

An adverse drug reaction is defined by World health organization as '' Any response to the drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy''.

An adverse cutaneous reaction caused by drug is any undesirable change in skin, its appendages or mucous membrane and it encompass all adverse effects related to drug eruption, regardless of etiology.

The pattern of adverse cutaneous reactions to drugs keep changing every year in accordance to emergence of newer drugs. There is a wide spectrum of cutaneous adverse drug reactions varying from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN) reported with imatinib. Hence the aim of my study is to evaluate the clinical spectrum of Cutaneous Adverse Reactions(CADRs) due to imatinib in our population.

AIM OF THE STUDY

AIM OF THE STUDY

To evaluate the pattern of cutaneous adverse reactions occurring in cancer patients on imatinib mesylate.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Imatinib mesylate is a 2-phenyl amino pyrimidine derivative that functions as a specific inhibitor of number of tyrosine kinase enzymes. Imatinib binds to an intracellular pocket located within tyrosine kinases (TK), thereby inhibiting ATP binding and phosphorylation and subsequent activation of growth receptors and their d ownstream signal transduction pathways .

Tyrosine kinases are enzymes that catalyze the phosphorylation of tyrosine residues on protein substrates. Tyrosine kinases are key components of signaling pathways including proliferation, differentiation, migration, and survival of cells.

The human genome encodes 90 Tyrosine kinases, which is divided into two main classes: receptor tyrosine kinase and non receptor tyrosine kinase.[73]

Receptor Tyrosine kinases are transmembrane proteins consists of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain containing the catalytic components. Receptor TKs are platelet-derived growth factor (PDGF) receptor (PDGFR), vascular endothelial growth factor (VEGF) receptor (VEGFR), epidermal growth

factor (EGF) receptor (EGFR), fibroblast growth factor receptor, and the rearranged during transfection (RET) kinase.[74]

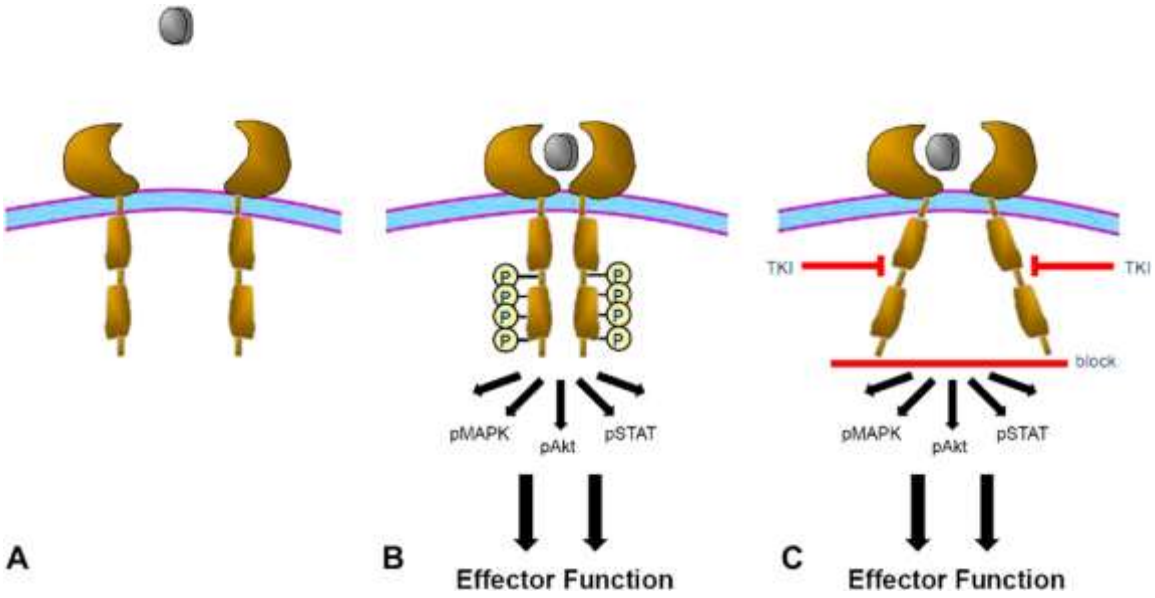


Figure 1

A.In absence of ligand binding, receptor TKs usually exists in cmonomeric and nonphosphorylated form.

B.Ligand binding to extracellular domain causes conformational changes that induce and stabilize receptor TKs, leads to autophosphorylation of their cytoplasmic domains. Activated tyrosine kinase catalyzes transfer of phosphate groups (P) to substrate molecules results in signal transduction,through mitogen-activated protein kinases (MAPKs), Akt, and STATs, and downstream effector functions.

C.In presence of TK inhibitor (TKI), cytosolic components of receptor TK fail to autophosphorylate, which prevents signal transduction and effector function.

Nonreceptor TKs lack extracellular and transmembrane domains and are activated by signals that cause either their dissociation from inhibitors or the phosphorylation of tyrosine residues within the TK complex.[75] The nonreceptor TKs are Abelson (Abl), sarcoma (Src), and janus kinase (JAK).

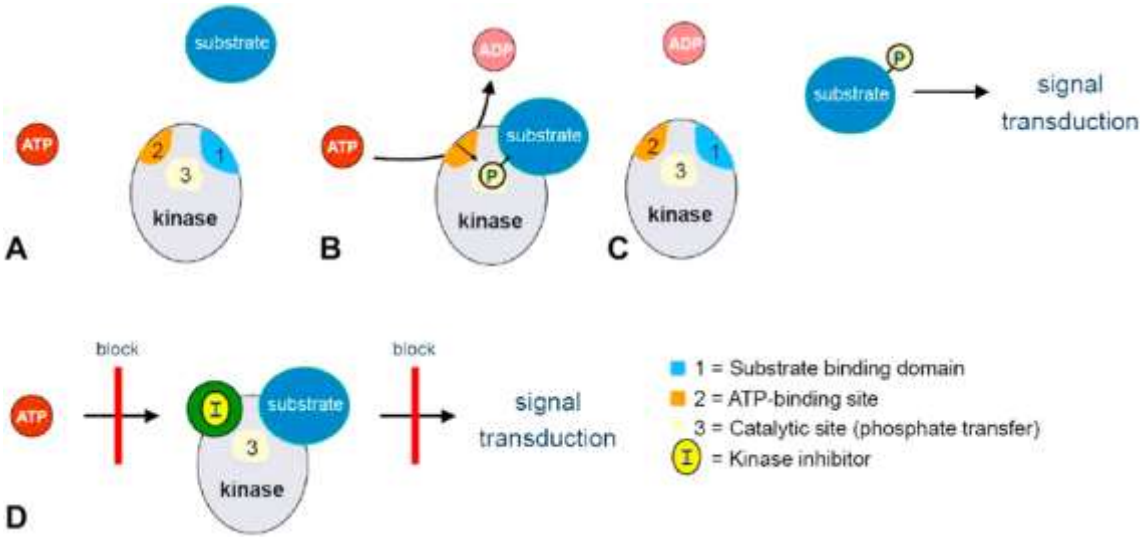


Figure 2

Activation of tyrosine kinxases (TKs).

A.TKs contain substrate-binding domain, adenosine triphosphate (ATP)-binding site, and catalytic site where phosphate group (P) will be transferred. Substrate is molecule to which phosphate will be transferred. Under basal conditions, TKs exist in inactive (‘‘closed’’) conformation

and phosphorylation of TKs stabilizes active (‘‘open’’) kinase conformation which leads to catalytic transfer of P to substrate molecules.

B.Activated TK transfers P from ATP (or guanosine triphosphate) to tyrosine residue on substrate molecule.

C.Phosphorylation of substrates by TKs is important cellular mechanism by which signal is propagated from one part of cell to another and leads to various effector functions.

D.Tyrosine kinase inhibitors usually bind kinase at ATP-binding site, thus prevents ATP from binding and transferring P to substrate, and consequently preventing active substrate from signaling to other parts of cell.

Imatinib is specific for tyrosine kinase domain in BCR- ABL,c-kit and Platelet derived growth factor (PDGF) receptors. Imatinib mesylate has been related to both cutaneous side effects and hypersensitivity reactions. The majority of these seems to directly depend on its mechanism of action, namely inhibition of physiologic function of cutaneous protein kinases, and appear to be dose dependent.

INDICATIONS

1.FDA approved:-

- Chronic myeloid leukemia (CML)
- Gastrointestinal stromal tumors(GIST)

2.Off label Indications:-

- Dermatofibrosarcoma protuberans
- Systemic sclerosis
- Systemic mastocytosis
- Melanoma
- Hyper eosinophilic syndrome.

Table 1. Therapeutic Targets of Imatinib in different diseases in which it is Used

Chronic Lymphocytic Leukemia	Bcr-abl
Gastrointestinal stromal tumor	c-kit
Hypereosinophilic syndrome	PDGFR
Systemic mastocytosis	PDGFR
Dermatofibrosarcoma protuberans	COL1A1PDGF
Melanoma	c-Kit
Systemic sclerosis	PDGFR

Adverse cutaneous drug reactions due to imatinib includes

I. Adverse reactions in the skin

II. Hair abnormalities

III. Nail changes

IV. Mucous membrane changes

ADVERSE REACTIONS IN SKIN

1. Acneiform eruption

2. Acute generalized exanthematous pustulosis

3. DRESS Syndrome

4. Facial edema

5. Erythema

6. Exfoliative dermatitis

7. Hand foot syndrome

8. Hypopigmentation

9. Lichen planus

10. Lichenoid eruption

11. Neutophilic eccrine hidradenitis

13. Palmar plantar hyperkeratosis

14. Petechiae

15. Photosensitivity

16. Pigmentation

17. Pruritus

18. Psoriasis

19. Rash

20. Stevens Johnson syndrome

21. Toxic epidermal necrolysis

22. Xerosis

23. Erythema nodosum

24.Pseudoporphyria

25.Kaposi sarcoma

26.Urticaria

27.Angioedema

HAIR

1. Alopecia

2. Follicular mucinosis

NAILS

Nail dystrophy

Nail pigmentation

MUCOSAL

1. Oral lichenoid eruption

2. Oral pigmentation

3. Oral ulcer

TABLE II : Skin reactions associated to imatinib according to the presumed pathogenetic mechanisms[2]

Dose dependent reactions	Hypersensitivity reactions
Alopecia	Urticaria
yschromia	Angioedema
Erythema	Anaphylaxis
Hand foot skin reaction	Stevens –Johnson syndrome/TEN
Papulopustular rash	Acute exanthematous pustulosis
Exfoliative dermatitis	Drug Related Eosinophilia And Systemic Syndrome(DRESS)
Xerosis	Neutrophilic dermatitis

Table III. Classification of Severity of Adverse Cutaneous Reactions Most Frequently Associated With Imatinib Use: United States National Cancer Institute Scale Version 4, Which Classifies Severity According to 4 Grades.

Grades	Macular-Papular Rash	Periorbital Edema	Skin Hyperpigmentation	Skin Hypopigmentation
1	Macules/papules covering <10% body surface area with or without symptoms (eg pruritus, burning, tightness)	Soft or non-pitting	Hyperpigmentation covering< 10% of body surface area; no psychosocial impact	Hypopigmentation or depigmentation < 10% of body surface area; no psychosocial impact

2	Macules/papules covering 10%-30% body surface area with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living	Indurated or pitting edema; topical intervention indicated	Hyperpigmentation > 10% of body surface area; psychosocial impact	Hypopigmentation or depigmentation > 10% of body surface area; psychosocial impact
3	Macules/papules covering >30% body surface area with or without associated symptoms; limiting self-care activities ofdaily living	Edema associated with visual disturbance;increased intraocular pressure, glaucoma or retinal hemorrhage;optic neuritis; diuretics indicated; operative intervention indicated		
4	-	-	-	-

Hypopigmentation

Hypopigmentation is more likely to be observed in dark-skinned patients. As the majority of patients in the Imatinib trials were white, this adverse effect was not observed frequently except in a few patients of African origin. Nevertheless it has been reported in a few white patients.[37,38] In a report from Malaysia, Leong et al reported the development of skin hypopigmentation in 65% of their CML patients treated with Imatinib[39]Pathogenesis of skin hypopigmentation by Imatinib is not fully understood, but involves the blockade of the c-kit (KIT) receptor tyrosine kinase pathway. Receptor c-kit and its ligand stem cell factor (SCF) have an important role in the homeostasis and in the development and survival of melanocytes. C-kit and stem cell factor also have an important role in migration of the melanoblasts from the neural tube to the skin during embryogenesis [40,41] . This is supported by the observation that human mutations in the encoded tyrosine kinase region of c-kit cause piebaldism, an autosomal dominant disorder characterized by white hair and hypopigmented skin patches on the forehead, torso, and extremities.[42] In adddition, murine models with human xenograft skin were subjected to c-kit inhibitory antibody (K44.2), which led to melanocyte loss and a decrease in differentiation antigens and melanocyte dendritic processes. Prolonged c-kit inhibition led to melanocyte

apoptosis.[43,44]These findings provide evidence of a critical role for SCF/KIT in the homeostasis and survival of human melanocytes.

Imatinb inhibits c-kit and by doing so seems to inhibit melanocytes, which can very well explain the development of hypopigmentation. Why some patients develop hypopigmentation, while others have no effect on their skin and whether those patients who do not develop skin lightening may be at a higher risk of relapse are unresolved questions. There was no evidence for correlation between development of hypopigmentation and efficacy of drug .

Imatinib was recommended to continued indefinitely in responding patients.[45]For this reason the number of patients taking Imatinib will continue to rise. In the future, this is likely to increase the number of pattients who develop skin hypopigmentation. There are important psycho-social implications of this phenomenon. It may not be acceptable to patients from certain racial backgrounds and may cause social embarrassment. On the contrary, whitening of the skin may be welcome in certain communities. This may render Imatinib for potential abuse. Particularly patients with dark skin should be warned of this adverse effect before commencing Imatinib treatment. In authours opinin, if hypopigmentation of the skin causes significant disturbance to the patient, it may be an indication to switch to a second line TK inhibitor.

This skin lightening effect of Imatinib may have at least one therapeutic potential. Patients with vitiligo and patchy hypopigmentation may benefit .A generalized hypopigmentation would be useful in these patients to make the patchy areas less conspicuous, particularly on the exposed parts of the body [46].

Hyperpigmentation

Paradoxical hyperpigmentation of the skin and abnormal pigmentation involving hair and nails have also been recorded Melasma is recorded in 19% of patients on imatinib in one study[47]. Melasma can be either localized, diffuse or sometimes have a characteristic pattern. The exact mechanism for hyperpigmentation is not fully understood. Imatinib can also cause hyperpigmentation by chelating one of its metabolites with iron and melanin a mechanism similar to minocycline and antimalarial-associated hyperpigmentation

Imatinib causes diffuse over stimulation of melanogenesis in the skin. How the same drug can produce both hypopigmentation and darkening in the skin is unclear, but a possible explanation may reside in it's binding to different receptors in the skin, some with activator and other with inhibitory effects on melanogenesis [24].

In a study of 118patients with CML treated with imatinib, only 4% developed hyperpigmentation.[49]

Acneiform eruptions

Acneiform eruptions are very rare with imatinib. Cystic acneiform eruption and follicular acneiform eruption have been documented.[3]

Earliest histopathological finding include a T-cell infiltrate around the follicular infundibulum followed by a suppurative folliculitis. In severe cases there may be granuloma formation with destruction of the hair follicle. In two patients focal acantholysis and neutrophilic infiltration around the eccrine coils have been noted. Microbiological culture is usually negative but occasional growth of Propionibacterium acnes and secondary infection with pathogenic staphylococcus has been documented.[4]

Cessation of offending drug will usually lead to complete resolution within a few weeks. Conventional acne therapy may be used, if treatment cannot be discontinued. Oral antibiotics such as doxycycline can be used in moderate and severe cases. In more severe cases, oral isotretinoin can be used.[5]

Acute generalized exanthematous pustulosis

Acute generalized exanthematous pustulosis (AGEP) is a rare cutaneous drug reaction involving T drug specific T lymphocytes and neutrophils. AGEP is a rare adverse effect of imatinib therapy and should be considered in patients who present with atypical rash on imatinib.[6]

Diagnostic Criteria for AGEP

1) Appearance of hundreds of sterile non follicular pustules at flexural sites between 2 and 5 days of drug intake .
2) Histopathological changes of spongiosis and epidermal pustule formation.
3) Fever >38 deg C
4) Blood neutrophil count >7* 10^9/L
5) Acute evolution

Exfoliative dermatitis

Imatinib induced exfoliative dermatitis usually occurs 1-3wks following initial exposure and within few hours to few days following a rechallange[7]. The exact mechanism is not known, but occurrence of skin eruption immediately after re-challenge suggest hypersensitivity rather than a pharmacological effect.There are only six probable cases of exfoliative dermatitis due to imatinib reported in literature[8,9]

Most of rashes due to imatinib are self limiting and do not require discontinuation of treatment. Oral antihistamines and topical steroids sufficient in most of these cases.

Lichenoid eruptions

The cutaneous lichenoid eruptions may be a result of the pharmacological effects of imatinib mesylate, and appear to be dose-

dependent. Lichenoid drug eruptions tend to be extensive, and may develop weeks or months after initiation of therapy. Lesions are rather more psoriasiform than in idiopathic lichen planus, and oral involvement is rare. Sun exposed areas such as extensors of extremities and dorsum of both hands are more commonly involved. As against classical lichen planus, lichenoid drug eruptions tend to be larger in size, less monomorphic and associated with scaling and crusting. Further classic sites of lichen planus like flexures and mucosa are not commonly involved in lichenoid eruptions. Histology is similar to classic lichen planus except for focal parakeratosis and presence of eosinophils and plasma cells in the dermis. . The difference between dug induced lichen planus and lichenoid drug reactions have not been discussed in any literature.

Resolution of the skin eruption may be slow after cessation of therapy, which is on average from 1 to 4 months, but up to 24 months in some cases.[4]

Hand foot syndrome

Hand foot syndrome is also known as palmoplantar erythrodysesthesia or acral erythema. It manifests as painful erythema of the palms and soles,with or without bullae. Dysesthesis (altered sensation of skin) may precede the symptoms.Clinically there are discrete

erythematous or violaceous patches or edematous plaques that arise on the palms and soles and may progress to involve the dorsal surfaces of the hands and feet. Rarely the eruption may be more extensive with truncal involvement.

On histological analysis hand-foot skin reaction shows several distinct features. In almost all patients there is keratinocyte damage which presents as intracytoplasmic eosinophilic bodies,vacuolar degenarartion of the keratinocytes and confluent keratinocyte necrosis leading intraepidermal cleavage. Papillomatosis and acanthosis may be seen indicating accelerated epidermal cell replication. Prominent parakeratosis with retention of pyknotic nuclei of epidermal cell is also seen indicating increased keratinocyte proliferation.

The exact mechanism behind acral erythema with painful blistering of palms and soles remains unclear. The fact that the incidence and severity of the rash increases with the dose implies that they are not due to allergic reaction. Proposed mechanisms include direct cytotoxic effect of the drug on eccrine sweat glands and increased blood flow to trauma prone sites leading to increased concentration of drug at the site. However acral erythema occuring at non trauma prone sites like finger webs and lateral aspect of sole remain to be explained. Imatinib induced acral erythema there is vacuolar degeration of keratinocytes present in the malpighian layer with acanthosis of the epidermis.[4]

Palmoplantar erythrodysthesia is usually managed by wound care,cold compresses,elevation of extremities and analgesics.Topical treatment with emollient or corticosteroids is often sufficient to relieve symptoms.

DRESS syndrome

Drug reaction with eosinophilia and systemic symptoms is a severe life threatening drug induced hypersensitivity reaction , characterized by skin rashes,fever, diffuse lymphadenopathy along with hypereosinophilia and elevated liver function tests. It usually occurs within two to six weeks of introducing drug .Severe cases may lead to fulminant hepatic failure and death.

The pathogenesis of DRESS syndrome is partially understood.Following mechanisms are suggested as possible pathophysiology:[10]

A) Reactivate metabolite formation and genetic defects to metabolize it

B) Intercurrent disease process.

C) Viral reactivation,mainly HHV-6

D) Dynamic cytokine profile

E) The Pi-Concept

DRESS can be treated with systemic steroids with favorable outcome.

Facial edema

Periorbital odema has been reported in upto 70% of patients treated with imatinib mesylate.[11]Platelet derived growth factor β is thought to regulate tissue fluid properties and avidly expressed on dermal dendrocytes of periorbital tisue. Studies have shown that inhibition of platelet derived growth receptor β in dermal dendrocytes by imatinib increases interstitial fluid pressure in dermis predisposes to edems[11,12] It has been suggested that the dense collagenous orbital septum and poorly developed lymphatic system of the orbit predispose this region to edema

Perorbital edema secondary to imatinib is typically mild to moderate and can be managed conservatively. Severe cases of periorbital edema treated by low salt diet, topical 1%hydrocortisone, 0.25% topical phenylephrine or oral diuretics.[13,14]Severe periorbital edema is not an indication for cessation of imatinib .For visually obstructive periorbital edema refractory to medical management, surgery remains a viable option.

Pityriasis rubra pilaris

Imatinib has been shown to interfere with regulatory T cells (Tregs) and the T-cell receptor signalling pathway, by reducing the phosphorylation of a leucocyte-specific protein tyrosine kinase, thereby changing the behaviour of the immune system in predisposed patients.

[15]Because dysregulation of the immune system (particularly the T-lymphocyte subsets) is also involved in the pathogenesis of PRP,[16] interference with T-cell function may be a feasible explanation for the PRP-like reaction.

Treatments included topical corticosteroid, ststemic corticosteroids ,keratolytics and retinoids.

Psoriasis

Deguchi et al. reported three cases with psoriasiform palmoplantar hyperkeratosis after long-term imatinib mesylate treatment.In two cases, nail dystrophy was also present. In three cases, discontinuation or dose reduction of imatinib mesylate led to the improvement of all lesions. They reported that hyperkeratotic lesions revealed psoriatic findings, but that the mechanism of action was unclear.[17]

Psoriasis an immune disorder in which T lymphocytes plays a primary role in pathogenesis. Imatinib affects cytokine production and proliferation of T cells and inhibits the secretion of interferon by T effector cells. These effects, together with imatinib suppression of c-kit and PDGF receptors, may help to explain the exacerbation of psoriasis in some patients

However, a case was published in which psoriasis improved in a patient with a GIST who was started treatment with 400 mg/d of imatinib.[18]

Erythema nodosum

The Erythema Nodosum is the prototype of panniculitis,. The pathogenesis of Erythema Nodosum is not fully elucidated. It is likely a delayed hypersensitivity reaction, which can be triggered by a variety of infectious and non-infectious antigenic stimuli including drugs like it would be the case with your patient [19]

The Eryethema Nodosum is clinically characterized by the unexpected appearance of painful, warm, erythematous, slightly raised nodules, measuring one to five centimeters in diameter and may coalesce to form plaques. Usually, these lesions undergo a bruise-like transformation and disappear after two to eight weeks without leaving scars [20,21]

Most common site involved is extensor aspect of legs.However, all body parts can be affected as the ankles, the thighs, the forearms, the face, the neck and the trunk [22,23]

Only one case of Imatinib-induced Erythema Nodosum has-been described in the literature by Drummond et al. This was a patient with tender subcutaneous nodules that were clinically and histologically

consistent with EN, not controlled with oral prednisilone and azathioprine,ultimately required discontinuation of the therapy [24]

Neutropholic eccrine hidreadenitis (NEH)

Neutrophilic eccrine hidradenitis is an uncommon inflammatory dermatosis usually seen in chemotherapy. It presents with fever and non specific cutaneous lesions. Clinically the lesions present as solitary or multiple, erythematous or purpuric macules, papules or plaques. The lesions may occasionally be painful. The common sites involved include trunk, face extremities and palms. Onset of the lesions is usually ten days after medication with accompanying fever and neutropenia. The condition is self limited and resolves within 30 days.

Mechanism of NEH is not clear. Either it can be a direct toxicity of chemotherapeutic drugs on eccrine coils or it may be part of neutrophilic dermatosis spectrum like Sweet's syndrome.[4]

Histology shows neutrophilic infiltrates surrounding eccrine glands and eccrine epithelial cell hydrophic degeneation.In severely neutropenic patients neutrophilic infiltrate may be absent but still eccrine gland necrosis is seen[4].

Sweet syndrome

Two cases of Sweet syndrome have been reported in patients treated with imatinib, and in one case the temporal association was clear.[25,26]

P**almoplantar hyperkeratosis**

Kuraishi et al. reported a patient with palmoplantar keratosis 6 months after initiation of drug.[27]Degouchi et al. reported cases of palmoplantar hyperkeratosis with psoriasiform lesion with nail dystrophy in two cases. They reported that hyperkeratotic lesions revealed psoriatic findings, but that the mechanism of action was unclear.[17]

Photosensitivity

It is defined as abnormal sensitivity following sun exposure.Imatinib causes lightening and depigmentation of skin, that may alter the skin protection against ultraviolet exposure, with subsequent intolerance to sun exposure.

Ai Tamura et al. in 2007[50] showed an in vitro evaluation of photosensitivity risk related to genetic polymorphisms of human ATP – Binding Cassette (ABC) transporter ABCG and inhibition by drugs demonstrating an inhibition by imatinib on the ATP – Binding Cassette subfamily G member 2 (ABCG2)-mediated porphyrin transport with a significant enhancement of the cellular photosensitivity. Certain genetic

polymorphisms and/or inhibition of ABCG2 by drugs can enhance the potential risk of photosensitivity. Pharmacogenomic testing for ABCG2 genotypes of CML patients treated with Imatinib would provide a better assessment of the risk of photosensitivity.

Two studies have been published of several cases of photosensitivity in patients in long-term treatment with imatinib,[28, 29]as well as a case of photo-induced dermatitis.[30]

Pseudoporphyria

Pseudoporphyria is a disorder with clinical, histopathological and immunofluorescence features that are similar to porphyria cutanea tarda but without the biochemical porphyrin abnormalities. It presents as blistering and skin fragility on sun-exposed sites. Unlike porphyria cutanea tarda, hypertrichosis, hyperpigmentation, dystrophic calcification and sclerodermoid changes are seldom associated with pseudoporphyria.[30] The various causes of pseudoporphyria include ultraviolet A exposure, chronic renal failure/dialysis and a wide range of drugs, particularly nonsteroidal anti-inflammatory drugs, diuretics, antibiotics and retinoids.[31]

Imatinib has been implicated occasionally in causing both pseudoporphyria and porphyria cutanea tarda. We were able to find seven previously reported cases of imatinib-induced pseudoporphyria and three

cases of imatinib precipitated/reactivated porphyria cutanea tarda in the English literature,[31,32,33] Two cases which were originally reported as skin fragility and blistering due to imatinib were subsequently categorized as pseudoporphyria in a review by Mahon et al.[32,34,35]

The pathogenesis of pseudoporphyria may differ depending on the causative factor; however, ultraviolet A exposure seems to be a common prerequisite. Various patho-mechanisms have been hypothesized in the causation of imatinib-induced pseudoporphyria. It has been suggested that imatinib, by inhibiting c-kit signaling in skin, might disrupt normal melanocyte biology leading to decreased photoprotection.[31,32]A recent experimental study has proposed that direct photosensitization by imatinib or its metabolites is unlikely and that photosensitive disorders might be due to impaired melanogenesis or accumulation of endogenous porphyrins.[36]

Treatment of pseudoporphyria often includes discontinuation or reducing the dose of the offending drug or switching to a non-implicated drug and/or photoprotection. However, clinicians and patients have to reach a decision together, after weighing the adverse effects and therapeutic benefits of the implicated drug.

Xerosis

It is characterized by dryness, may or may not be associated with scaling.It is caused by the abnormal keratinocyte differentiation, which induces an altered stratum corneum, a decrease in moisture retention and a reduction in epidermal loricrin.

Treatment includes topical emollients and antihistamines.

Kaposi's sarcoma (KS)

Kaposi's sarcoma (KS) is a multifocal vascular proliferative disease involving predominantly the skin but that may also affect the mucosa and the viscera.[51,52] A human herpes virus type 8 (HHV8) associated with all types of KS. HHV8 contains several genes with homology to human oncogenes and growth factors [53] During in situ hybridization and in immunohistochemistry techniques, KS cells have been shown to express platelet-derived growth-factor receptor (PDGFR) and the proto-oncogene c-kit, a tyrosine kinase receptor. receptor. The former is involved in the induction of angiogenesis and cell growth. The latter, in response to c-kit ligand, stimulates the proliferation of HHV8-infected KS dermal microvascular endothelial cells in which this receptor is upregulated.[54]

Tyrosine kinases inhibited by imatinib are c-kit, the receptor for kit ligand, and the structurally similar PDGFR-α and PDGFR-α and -β

receptors. However, several cytokines and growth factors are involved in KS progression.[54]The ability of KS cells to express both PDGF-α and -β receptors has already been shown, while c-kit—another tyrosine kinase receptor— is involved in the formation of KS cells. In the HHV8 KS cells, an upregulation of c-kit, resulting in proliferative and antiapoptotic effects, has been observed. This is why c-kit is a target for the pharmacologic intervention of imatinib.[54]Elena Campione .et al[55/]reported Kaposi's Sarcoma in a Patient Treated With Imatinib Mesylate. for Chronic Myeloid Leukemia.

Rashes

Skin rashes are a possible side effect of imatinib therapy, and they are observed more frequently in women. In many cases, the lesions are mild, limited and may easily be treated with an antihistaminic or topical steroid. However, in serious cases, the use of a short-term oral steroid may be required[56]. According to some studies, rash is a frequent event and may present in up to 66.7% of patients within 2 months of starting the drug[57].

Imatinib-associated rashes are often pruritic. Lesions commonly arise in the form of erythematous or maculopapular lesions. They are generally observed in the forearm or body, and less frequently on the face. Skin biopsy may typically establish a toxic drug reaction[56]

Skin rashes may frequently be associated with the intake of imatinib (66.7%) [58.] However, grade 3 or 4 skin rashes are observed in only a small proportion of these cases (3.8%). In some patients, serious reactions may be observed in which the flaking of the skin occurred, and Stevens-Johnson syndrome has been reported [59,60.] In such cases, imatinib should be discontinued urgently, and systemic 1 mg/kg/day steroid therapy should be commenced. In serious skin lesions that are resistant to supportive therapies, imatinib therapy should be discontinued. However, this situation is observed in fewer than 1% of all patients who take imatinib[56]

Stevens-Johnson Syndrome

Several cases of SJS have been reported in patients treated with imatinib.[60-63]Hsiao et al.[60]described a patient with CML who developed signs and symptoms reminiscent of SJS one week after starting the drug. These resolved after with-drawal of the drug and reappeared on rechallenge, strongly suggesting that the drug played a role in the eruption. In a study conducted by Pavithran K et, however, the eruption did not appear after rechallenge at lower doses.[62]

In another case report of SJS, a patient treated with400 mg/d of imatinib underwent rechallenge at a dose of200 mg/d and the lesions reappeared.[64]

At a second rechallenge at a dose of 100 mg/d and 1 mg/kg/d of prednisone, the lesions did not reappear. On suspending prednisone after 6 weeks, the imatinib dose was increased to 300 mg/d with no adverse effects. Some authors suggest that desensitization should be attempted to manage these severe mucocutaneous eruptions when the lesions reappear even with concomitant useof prednisone.[65]

Toxic Epidermal Necrolysis

A case has been reported that the patient with CML who developed a very severe blistering skin and mucosal eruption after allogeneic bone marrow transplantation (with fludarabine and busulphan conditioning) and treatment with imatinib.[66]

Hair changes

Patchy hair loss is a rare drug-related side effect in patients receiving imatinib. Hair loss was characterized by follicular plugging, broken hair, hair depigmentation and thinning under dermoscopy, perifollicular inflammatory infiltration with relative sparing of interfollicular epidermis, and perifollicular basal vacuolization and clefts were well demonstrated by histopathology of scalp.[67]

Hair graying and mild hair loss in patients undergoing imatinib therapy was reported by few authors.[68,69]The mechanism of hair loss is related to inhibition of platelet-derived growth factor receptor (PDGFR),

which is responsible for inducing and maintaining of anagen phase of hair.[70]

Paradoxically, Etienne et al.4 reported hyperpigmentation of the hair in nine of 133 patients . Hair graying and mild hair loss in patients undergoing imatinib therapy was reported by a few authors. The mechanism of hair graying is related to inhibition of stem cell factor (SCF) and its receptor c-kit (CD117), which are responsible for survival, differentiation, and proliferation of the melanocyte.[71]

Nail pigmentation

Melanonychia is a darkening of the nail caused by deposition of melanin or other pigments occuring in two patterns- longitudinal melanonychia or transverse melanonychia. The mechanism of melanonychia is unknown. Potential causes include toxicity affecting nail bed or nail matrix,focal stimulation of nail matrix melanocytes and photosensitization.

The difference between longitudinal and horizontal pigmention lies in their focus of origin. Longitudinal melanonychia occurs as a consequence of two mechanism, one is due to melanocyte activation due to inflammation, infections,non melanocytic neoplasms genetic factors and drugs. The other mechanism is melanocyte hyperplasia caused by benign melanocytic nevi or malignant melanoma. Transverse

pigmentation of nail probably develops due to direct toxic effect on nail matrix.[72]

The mechanism of Imatinib induced pigmentation is remains obscure..Imatinib targets tyrosine kinases of BCR -ABL ,c-kit, PDGF receptor. c-kit is normally expressed in skin basal cells, melanocytes, epithelial cells of breast tissue and mast cells.It has a regulatory role in melanogenesis, melanocyte homeostasis and pigmentation. Imatinib interferes in the function of c-kit, and thus may lead to stimulation of melanocytes in the visible portion of distal nail matrix.

Common nail changes acquired during treatment are mostly asymptomatic and thus require no treatment. But forewarning of the patients and early recognition of symptoms are essential to avoid unnecessary anxiety on the part of the patient.

Oral pigmentation

Generally, medication-induced melanosis in the oral mucosa can be attributed to any one of the following mechanisms: pigmented breakdown of drug products, drugs inducing melanin formation, or drug metabolites chelated with iron and melanin.

The pathogenesis of oral mucosal pigmentation in patients taking Imatinib still remains unclear; it has been suggested that Imatinib blocks the binding on the c-kit receptors (a growth factor receptor found on skin

cell,melanocytes, and mast cells) and subsequently alters both melanogenesis and melanocyte homeostasis. However, pigmented depositions in the oral mucosa indicate much different pathologies and are challenging to diagnose correctly. Differential diagnosis includes physiological pigmentation, amalgam tattoo, melanotic macule, smoker's melanosis, melanocytic nevus, malignant melanoma, and drug-induced melanosis.

The diagnosis of imatinib-related pigmentation depends on a thorough medical history and characteristic clinical presentation. The hyperpigmention are benign, and no treatment is required. Fortunately, the oral lesions occur on the hard palatal mucosa and are not of cosmetic concern.

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN:

Observational Prospective study.

STUDY POPULATION AND STUDY PERIOD:

Study was conducted in department of medical oncology, Government Rajaji hospital, Madurai medical college, Madurai All confirmed cases on Imatinib were enrolled in the study over a period of 7 months after obtaining clearance from institutional ethical committee.

MATERIALS:

All diagnosed cancer patients on Imatinib attending oncology OPD irrespective of age and sex were included in the study. Both written and informed consent were obtained from patients or guardian to carry out necessary investigations and to take clinical photographs.

Detailed history regarding residence, occupation, and treatment modalities were recorded. History pertaining to any drug reaction, if so, the reaction time, duration of reaction, previous allergic history, type of skin lesions was noted. Coexisting dermatological conditions and other medical ailments were obtained. A thorough drug history was recorded

related to all prescriptions and over the counter drugs during last month with date and dosages.

A detailed physical examination was performed and dermatological examination regarding morphological patterns, site of skin lesions were recorded in predesigned proforma. Relavant investigations were carried out. Patients were managed with appropriate treatment.

Severity of the reaction was assessed using CTCAE(Common Terminology criteria for Adverse Events) scale version 4.1. Causality of the drug was assessed using Naranjo Causality assessment scale.

STATISTICAL ANALYSIS:

CADRs were described according to their demographical and clinical variables in terms of percentages and averages in respect of categorical variables and continous variables respectively.

INCLUSION CRITERIA

All patients admitted for imatinib in medical oncology department, Government Rajaji hospital during the study period were included in the study.

EXCLUSION CRITERIA

Patient who had a previous history of any skin disease were excluded from this study.

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

The total number of patients with Chronic myeloid leukemia and Gastrointestinal stromal tumour on imatinib was 142.

1.TOTAL INCIDENCE OF CADRs

Out of total 142 patients who were enrolled in the study period of 6months, 55 paients had at least 1 CADR. The overall incidence of CADRs in this study was found to be 38.73%.

TABLE 1: TOTAL INCIDENCE OF CADRs

Total number of patients	No. of patients having atleast 1 CADRs	Nil dermatological manifestations
142	55(38.73%)	87(61.27%)

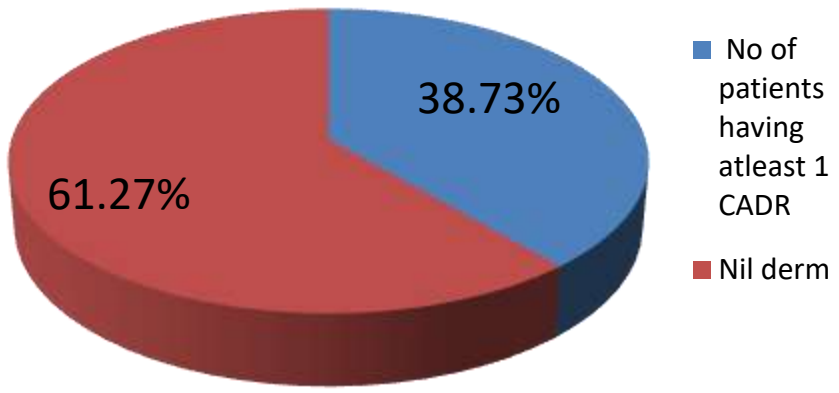


Figure 3

2. AGE PREVALENCE:

The age of patients varied from 12 to 85 with a mean age of 44.94% .56.34% of cases were in age group between 41 and 60;31.69% were in age group between 20 and 40;9.15% were above 60 years of age and 2.82% were less than 20 years of age.

Out of 55 pateients with CADRs, majority belonged to age group 41 to 60years (23.24%. the second most common age group affected was 20 to 40years (11.98%).Youngest age group affected was 12years in males and 20years in females.

TABLE 2: AGE PREVALANCE

AGE	Total no of cases	%	No of cases with CADRs	%
<20	4	2.82	2	1.40%
20-40	45	31.69	17	11.98%
41-60	80	56.34	33	**23.24%**
>60	13	9.15	3	2.11
TOTAL	142	100%	55	**38.73%**

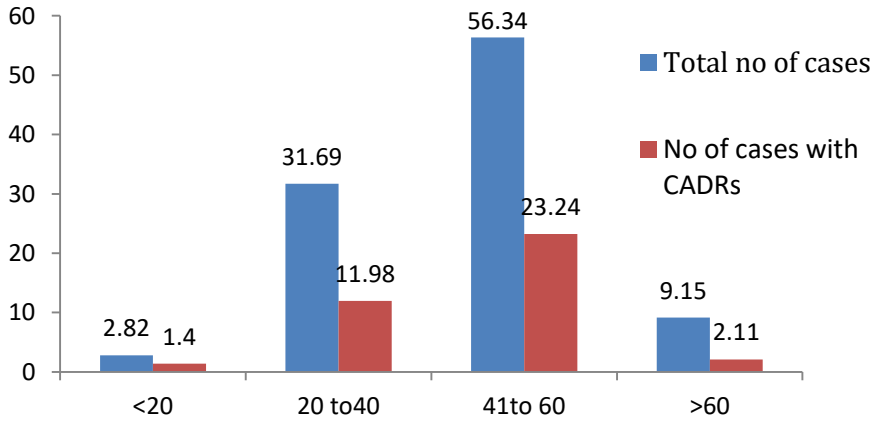


Figure 4

3. SEX PREVALENCE:

Out of 142 patients, 90 (63.12%) were males and 52 (36.88%) were females.

TABLE 3: SEX DISTRIBUTION

SEX	No. of cases	%
Male	90	63.12
Female	52	36.88
Total	142	100 %

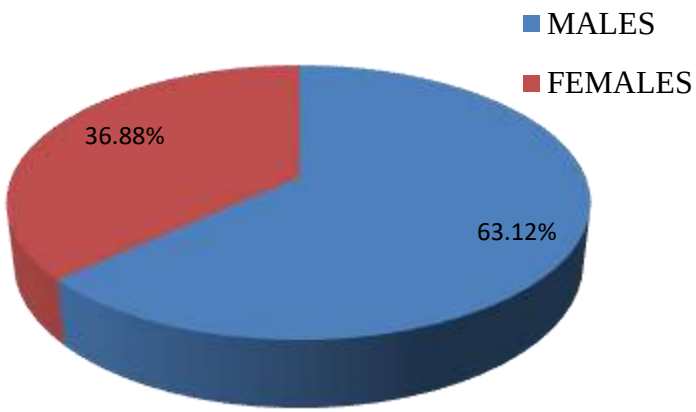


Figure 5

4. DURATION OF TREATMENT

The duration of treatment ranged from 3 months to 15 years. The duration was less than 6 months in 20 patients(14.08%), between 6 months to 5 years for 107 patients(75.35%) and more than 5 year for 15 patients(10.56%)

Duration of treatment	No of case	%
< 6 months	20	14.08
6 months- 5 year	107	75.35
>5 year	15	10.56
Total	142	100%

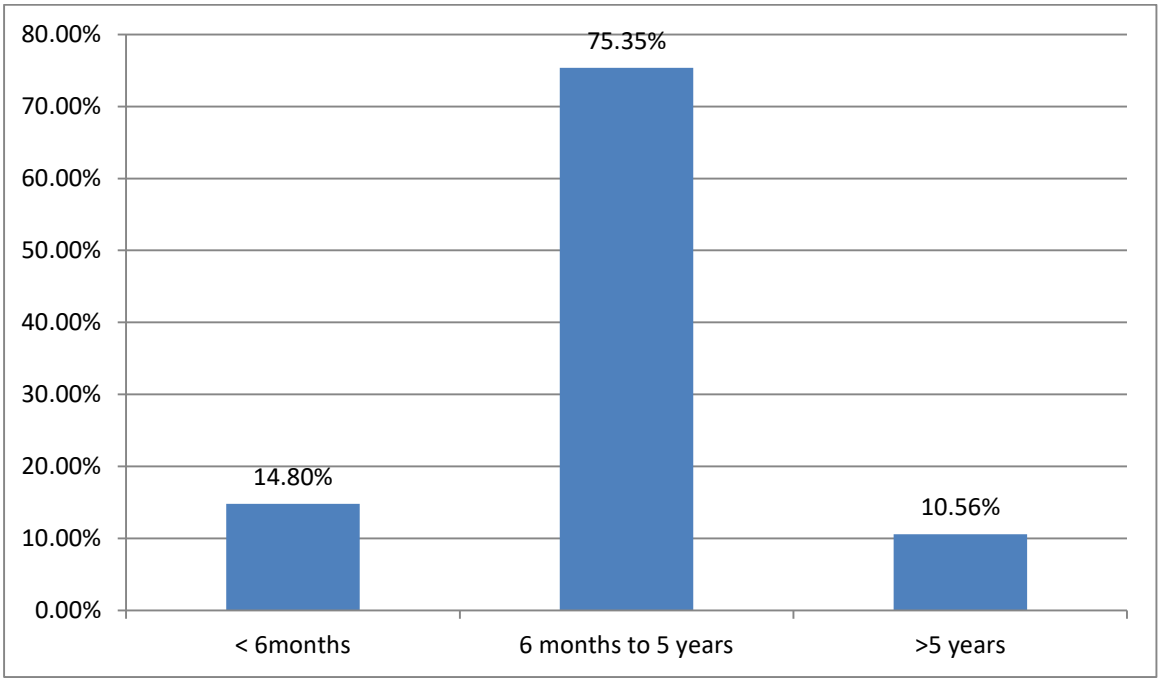


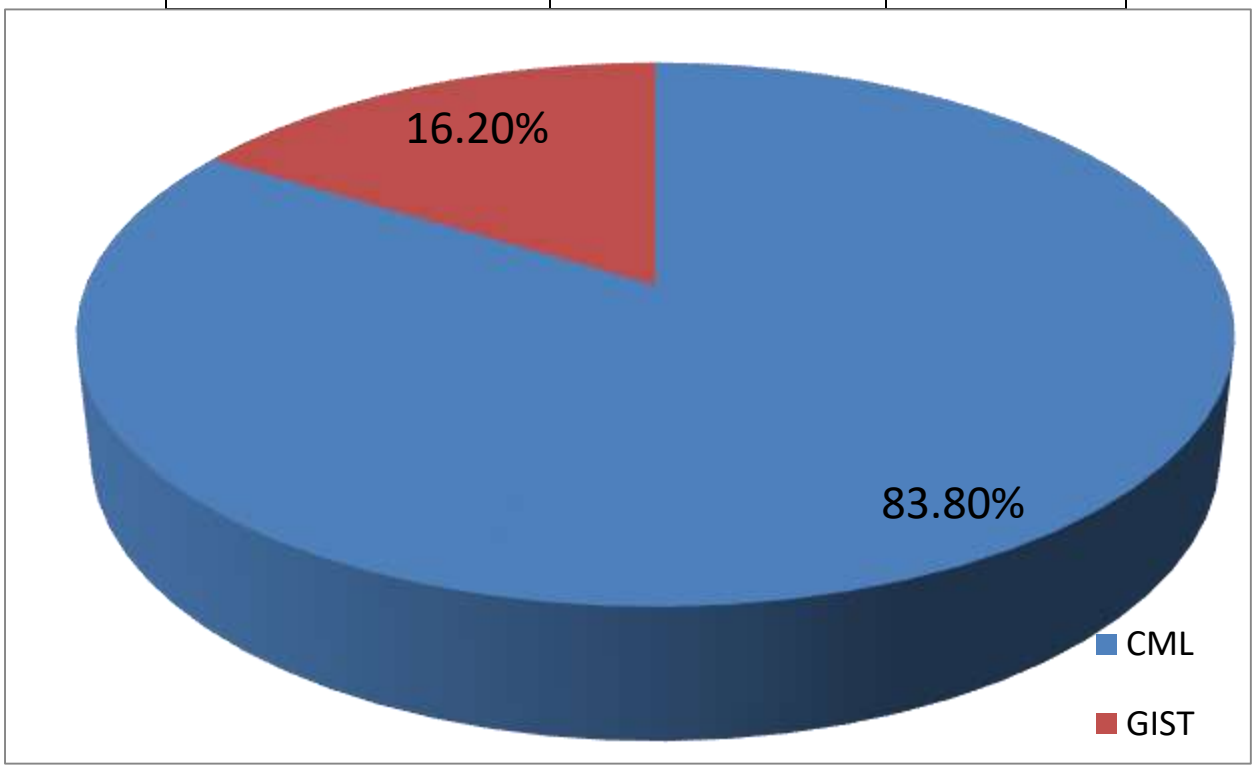
Figure 6

5. TYPE OF DISEASE

Out of 142 patients, 119 patients were CML and 23 patients were GIST

TABLE 5: TYPE OF DISEASE

Type of disease	No of cases	%
CML	119	83.80
GIST	23	16.20
TOTAL	142	100%



6. CLASSIFICATION OF SUBJECTS ACCORDING TO DISEASE

Out of 119 CML Patients, 80 (67.23%) were male and 39 were female. Out of 23 GIST patients, 10 were male and 13 were female.

TABLE 6: CLASSIFICATION OF SUBJECTS ACCORDING TO DISEASE

	Male	Female
CML	80(67.23%)	39(32.77%)
GIST	10(43.48%)	13(56.52%)

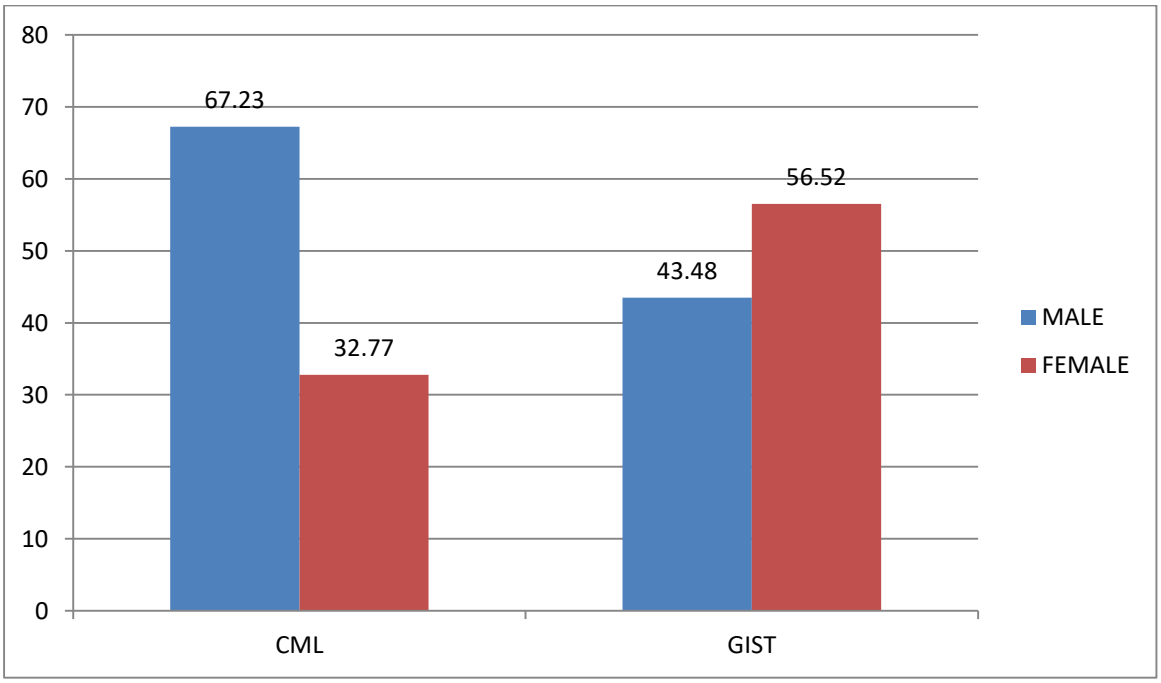


Figure 7

7. PREVALENCE OF CUTANEOUS EFFECTS AMONG CML PATIENTS

TABLE 7:PREVALENCE OF CUTANEOUS EFFECTS AMONG CML PATIENTS

Total no of CML cases	No. of cases with CADRs	Nil dermatological manifestations
119	**46 (38.66)**	**72 (61.34%)**

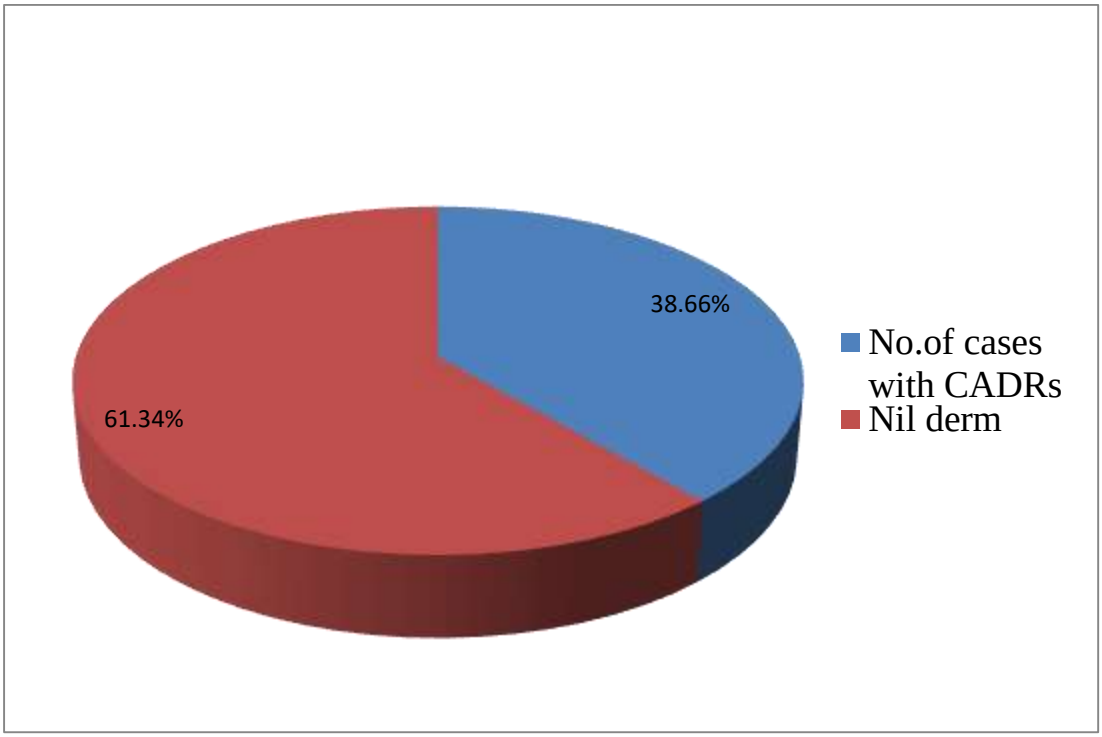


Figure 8

	Total No. of cases	No. of cases with CADRs
MALE	80	27(33.75%)
FEMALE	39	19(48.72)

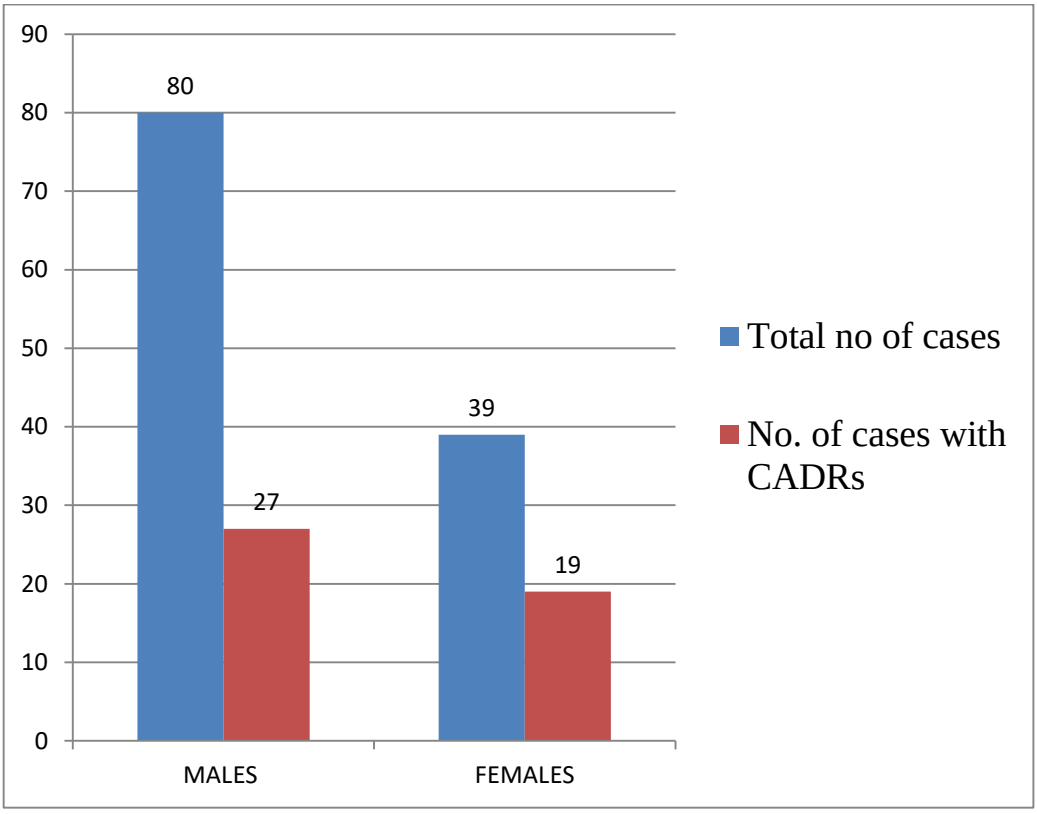


Figure 9

8. CUTANEOUS MANIFESTATIONS IN MALE CML PATIENTS

Total no. of males-80

	No. of cases	%
Hypopigmentation	**12**	**15**
Melasma	**8**	**10**
Lichenoid drug reaction	**2**	**2.5**
Erythroderma	**1**	**1.25**
Pruritis	**1**	**1.25**
Nail dystrophy	**2**	**2.5**
Pompholyx	**1**	**1.25**
Total	**27**	**33.75**

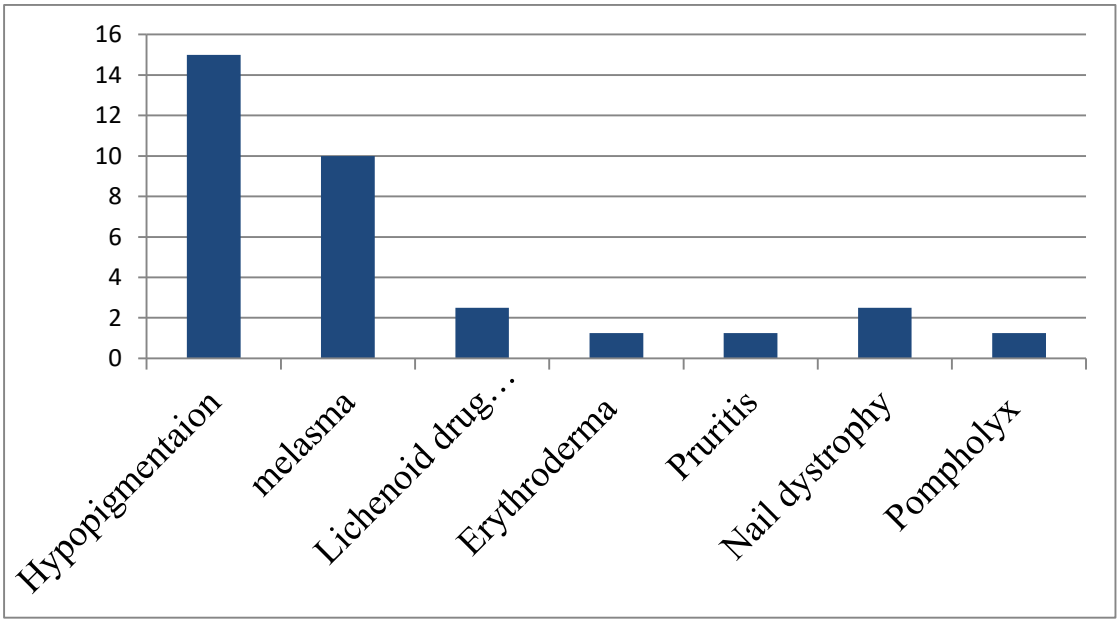


Figure 10

9. CUTANEOUS MANIFESTATIONS IN FEMALE CML PATIENTS

Total no. females-39

	No. of cases	%
Hypopigmentation	**7**	**17.94**
Melasma	**9**	**23.07**
Lichenoid drug reaction	**1**	**2.56**
Erythroderma	**1**	**2.56**
Nail pigmentation	**1**	**2.56**
Total	**19**	**48.69**

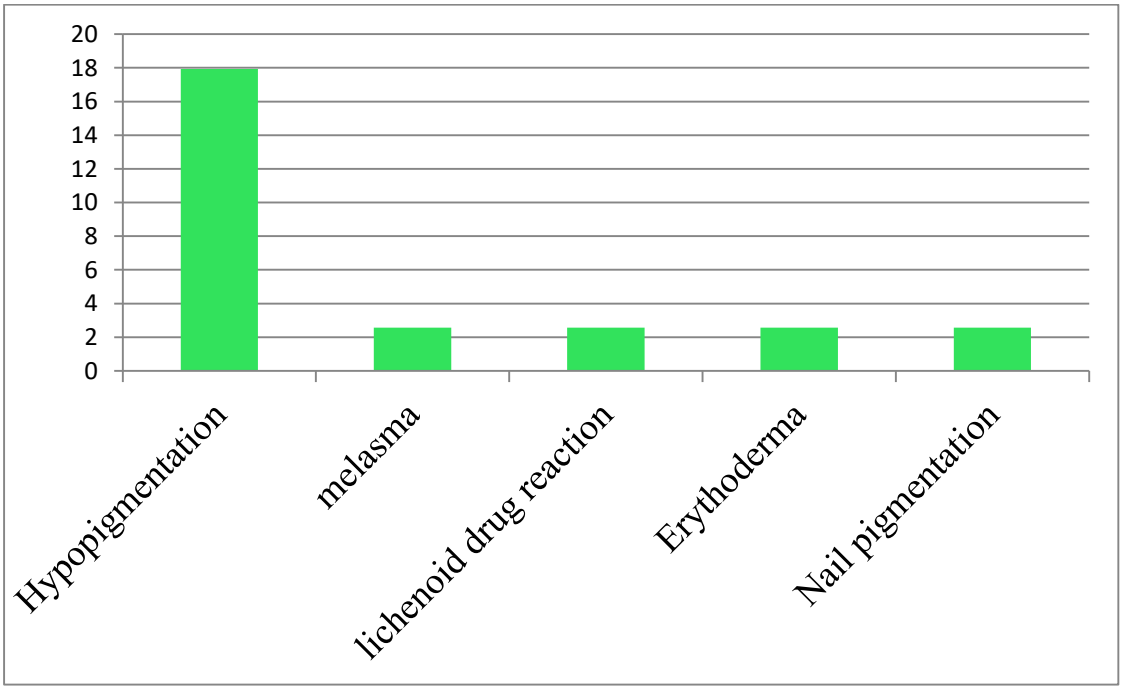


Figure 11

Total no. of CML patients were 119; 46 (38.66%) patients had atleast one CADRs and 72 (61.34%) with nil dermatological manifestations

Out of 80 males, 27 (33.75%) patients had at least one CADRs. Out of 39 females, 19(48.72%) patients had at least one CADRs.

Out of 80 males, 12 (15%) patients had hypopigmentation;8 (10% patients)had melasma; 2(2.5%) patients had lichenoid drug reaction; 1(1.25%) patient had erythroderma; 1 (1.25%)patient had pruritis; 2 (2.5%) had nail dystrophy; 1(1.25%)patient had pompholyx

Out of 39 females, 7 (17.94%) patients had hypopigmentation;9(23.07% patients) had melasma; 1(2.56%) patients had lichenoid drug reaction; 1(2.56%) patient had erythroderma; (2.56%) had nail pigmentation;

10.PREVALENCE OF CUTANEOUS EFFECTS AMONG GIST PATIENTS

Total no of GISTcases	No. of cases with CADRs	Nil dermatological manifestations
23	9 (39.13%)	14(60.87%)

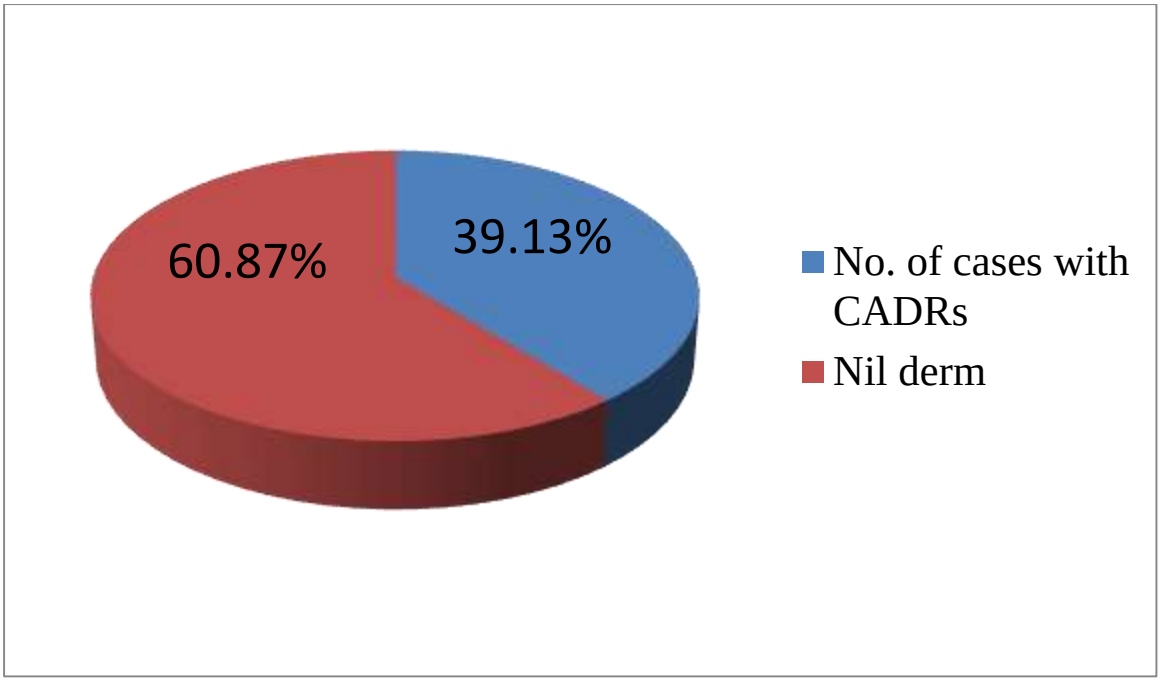


Figure 12

	Total No. of cases	No. of cases with CADRs
MALE	10	5 (50%)
FEMALE	13	4 (30.77%)

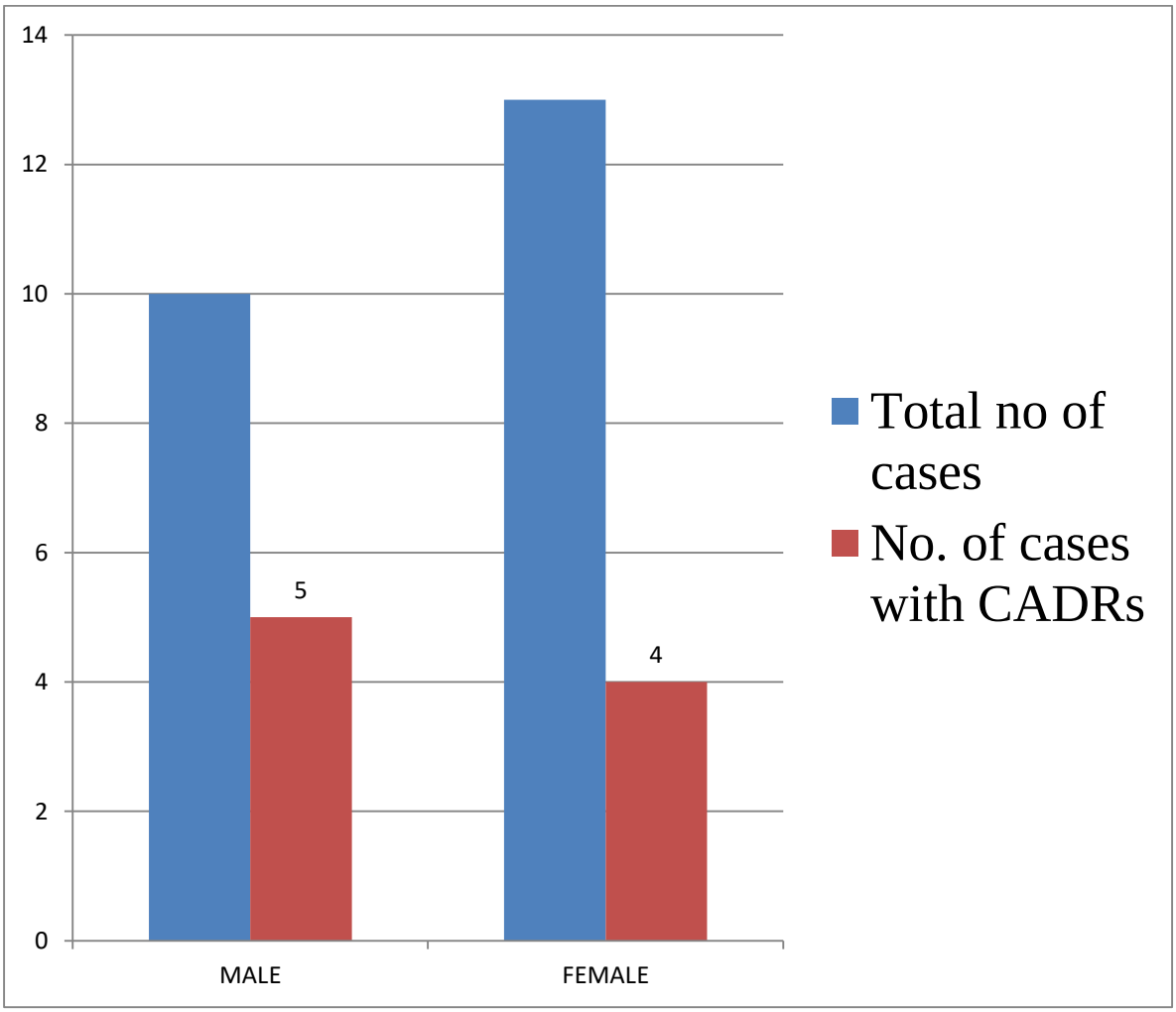


Figure 13

11.CUTANEOUS MANIFESTATIONS IN MALE GIST PATIENTS

Total no.of cases- 10

	No .of cases	%
Melasma	**3**	**30**
Hypopigmentation	**1**	**10**
Pruritis	**1**	**10**

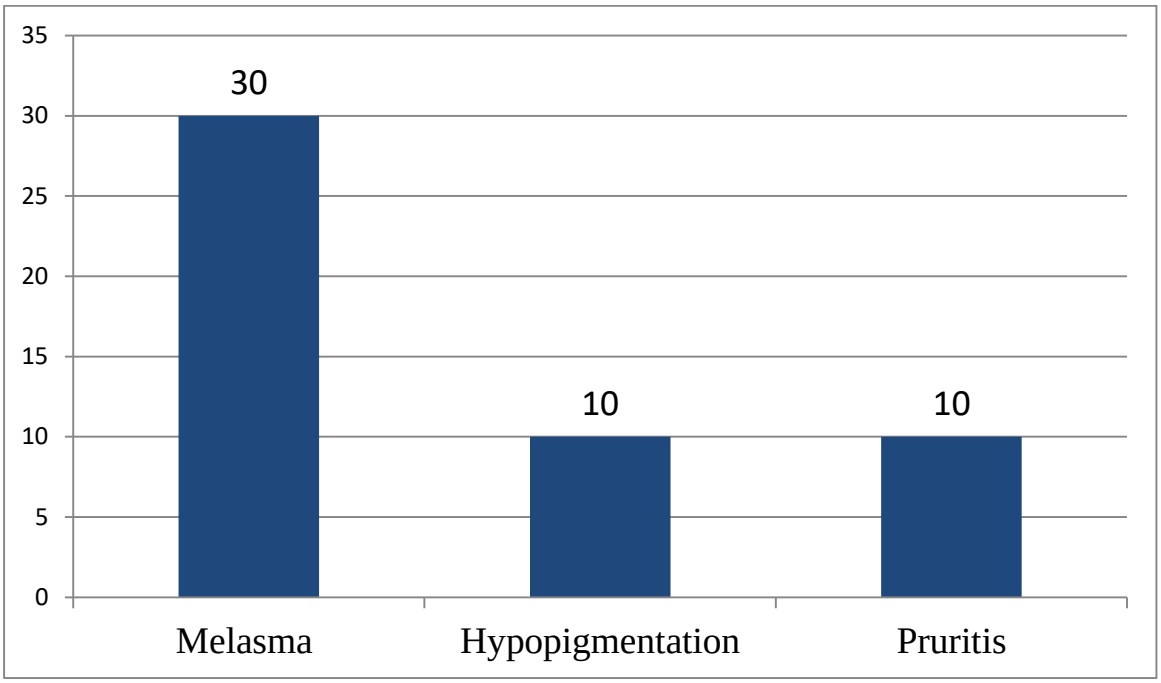


Figure 14

12.CUTANEOUS MANIFESTATIONS IN FEMALE GIST PATIENTS

Total no of cases-13

	No .of cases	%
Hypopigmentation	**3**	**23.1**
Melasma	**1**	**7.7**

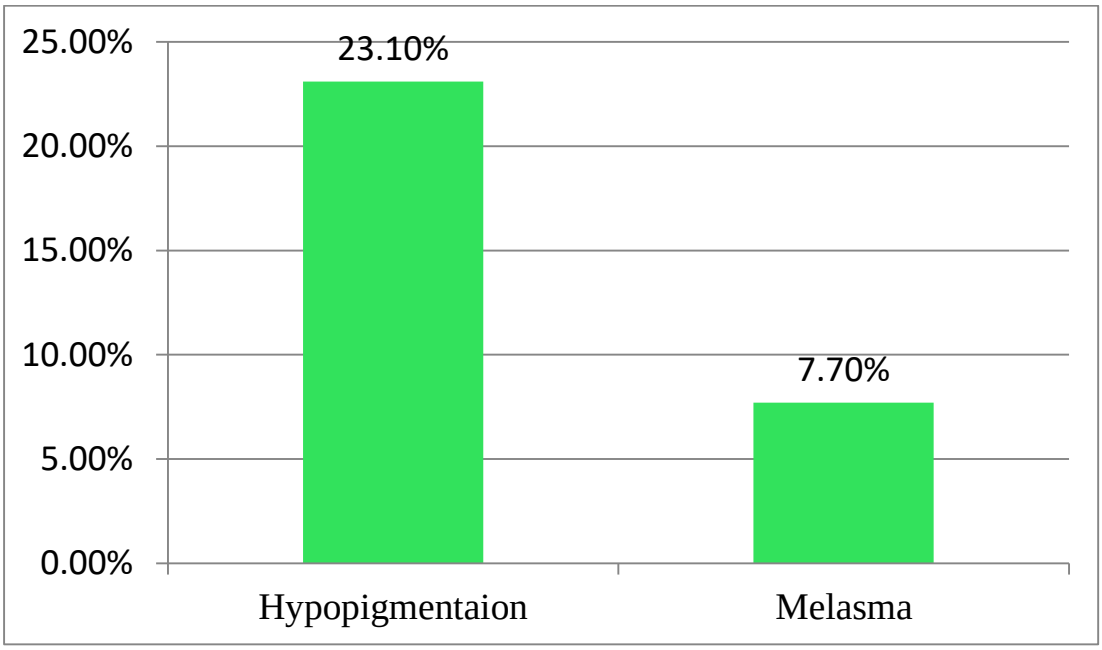


Figure 15

Total no. of GIST patients- 23; 9(39.13%) patients had atleast one CADRs;14(60.8%) with nil dermatological manifestations

Out of 10 males, 5(50%) had atleast one CADRs. Out of 13 females, 4 (30.77%) had at least one CADRs.

Out of 10 males, 1(10%) patients had hypopigmentation;3 (30%) patients had melasma; 1 (10%) patients had pruritis

Out of 13 females, 3(23.1%) patients had hypopigmentation: 1 (7.7%%) patient had melasma;

13. OVERALL PREVALENCE OF CUTANEOUS MANIFESTATIONS

Adverse effect	No	%
Hypopigmentation	23	16.22
Melasma	21	14.81
Lichenoid drug reaction	3	2.10
Erythroderma	2	1.40
Nail dystrophy	2	1.40
Itching	2	1.40
Pompholyx	1	0.70
Nail pigmentation	1	0.70
Total	55	38.73%

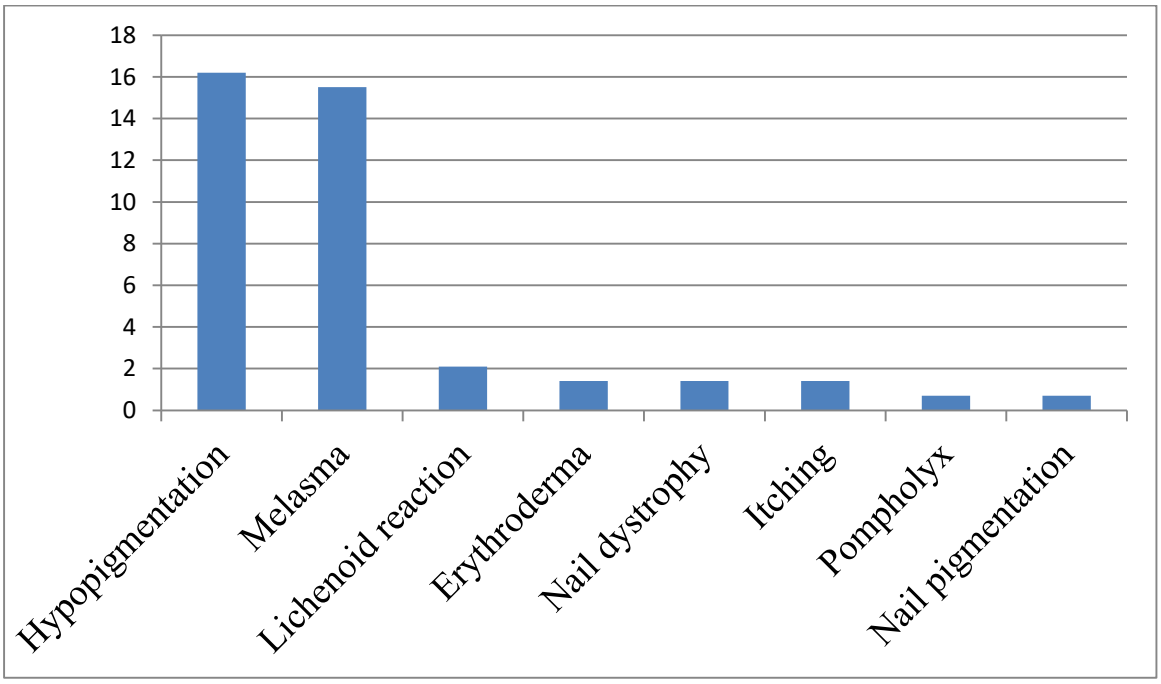


Figure 16

14. GENDERWISE PREVALENCE OF CUTANEOUS MANIFESTATIONS

	MALE		FEMALE		TOTAL	
	No. of MALE cases	%	No. of FEMALE cases	%	Total no. of cases	%
Melasma	11	7.76	10	7.05	21	14.81
Hypopigmentation	13	9.17	10	7.05	23	16.22
Lichenoid drug reaction	2	1.40	1	0.70	3	2.10
Erythroderma	1	0.70	1	0.70	2	1.40
Nail dystrophy	2	1.40	0	0	2	1.40
Itching	2	1.40	0	0	2	1.40
Pompholyx	1	0.70	0	0	1	0.70
Nail pigmentation	0	0	1	0.70	1	0.70
Total	**32**	**22.53%**	**23**	**16.20%**		**38.73%**

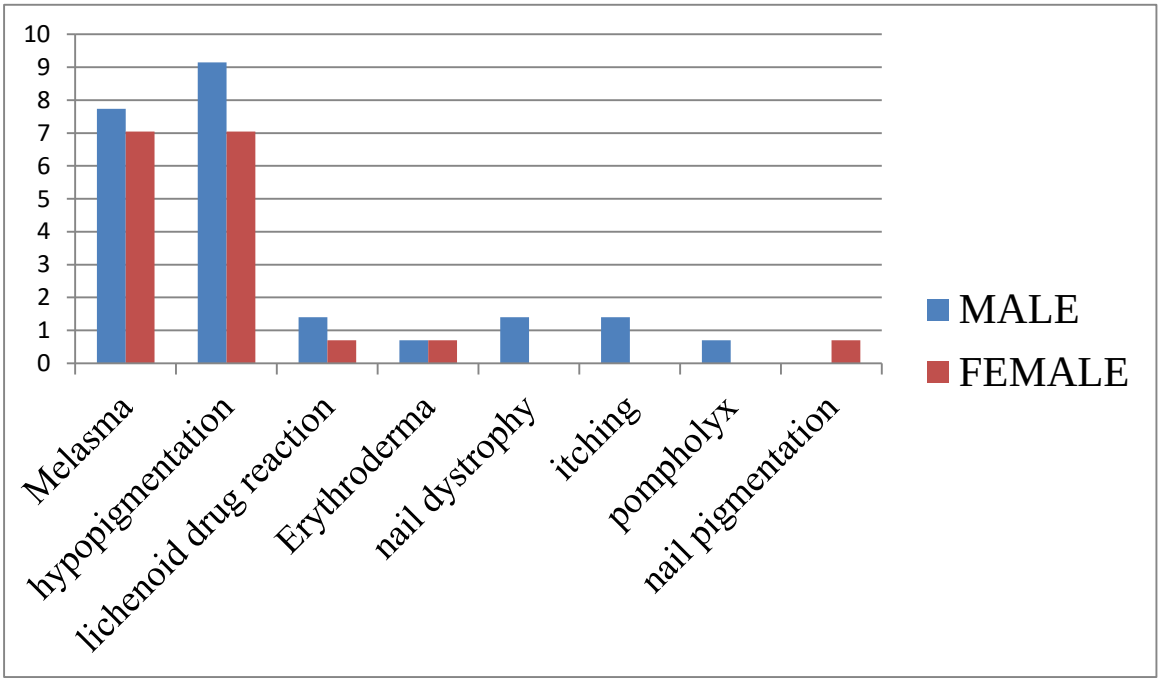


Figure 17

1.HYPOPIGMENTION

Out of 142 patients, 13 males (9.17%) and 10(7.05%) females had hypopigmentation. The total prevalence of hypopigmentation in both sexes was 16.20%

2.MELASMA

Melasma was noted in 21 patients (14.81%).It was noted in 11 males (7.76%) and 10 females (7.05%)

3.LICHENOID DRUG REACTION

Lichenoid drug reaction was observed in 3 patients(2.10%). It was noted 2males(1.40%) and 1 female (0.70%)

4.ERYTHRODERMA

Erythroderma was seen seen in 2 patients (1.40%). One case in male (0.70%) and one case in female(0.70%)

5. NAIL DYSTROPHY

Nail dystrophy was noted in 2 (1.40%)male patients only.

6. POMPHOLYX

One male case (0.70%) developed pompholyx

7.NAIL PIGMENTATION

One female case(0.70%) shown nail pigmentation

8.PRURITIS

Two male patients developed pruritis (1.40%)

15. TIME INTERVAL BETWEEN ONSET OF ADVERSE CUTANEOUS REACTIONS AND DRUG HYPOPIGMENTATION

Median time of onset – 4 months

Time of onset of hypopigmention	No. of cases
2 months	4
3 months	3
4 months	**4**
5 months	3
6 months	5
7 months	1
Not known	3
Total	**23**

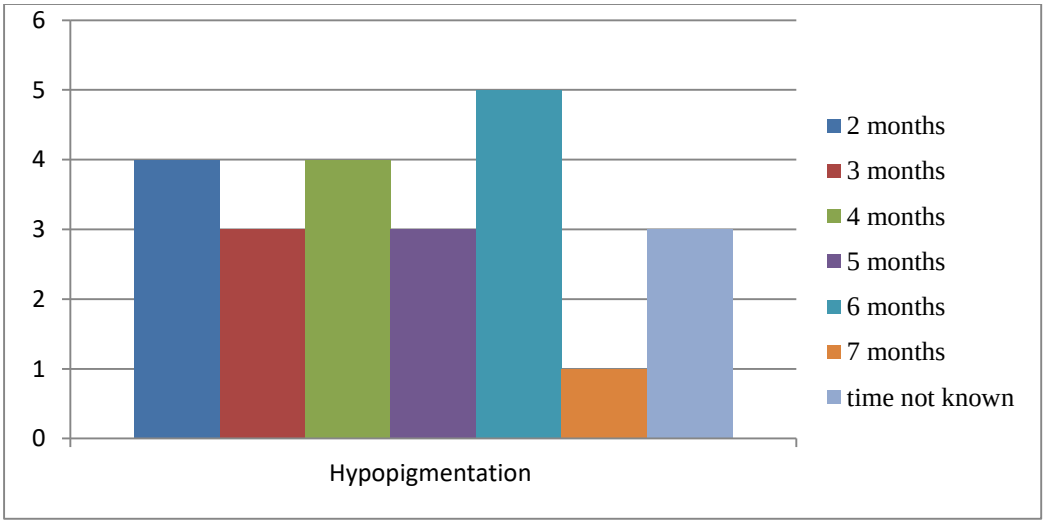


Figure 18

MELASMA

Median time of onset – 6 months

Time of onset of Melasma	No .of cases
1 months	2
2 months	2
3 months	3
4 months	2
6 months	**4**
7 months	1
8 months	1
12 months	6
Total	**21**

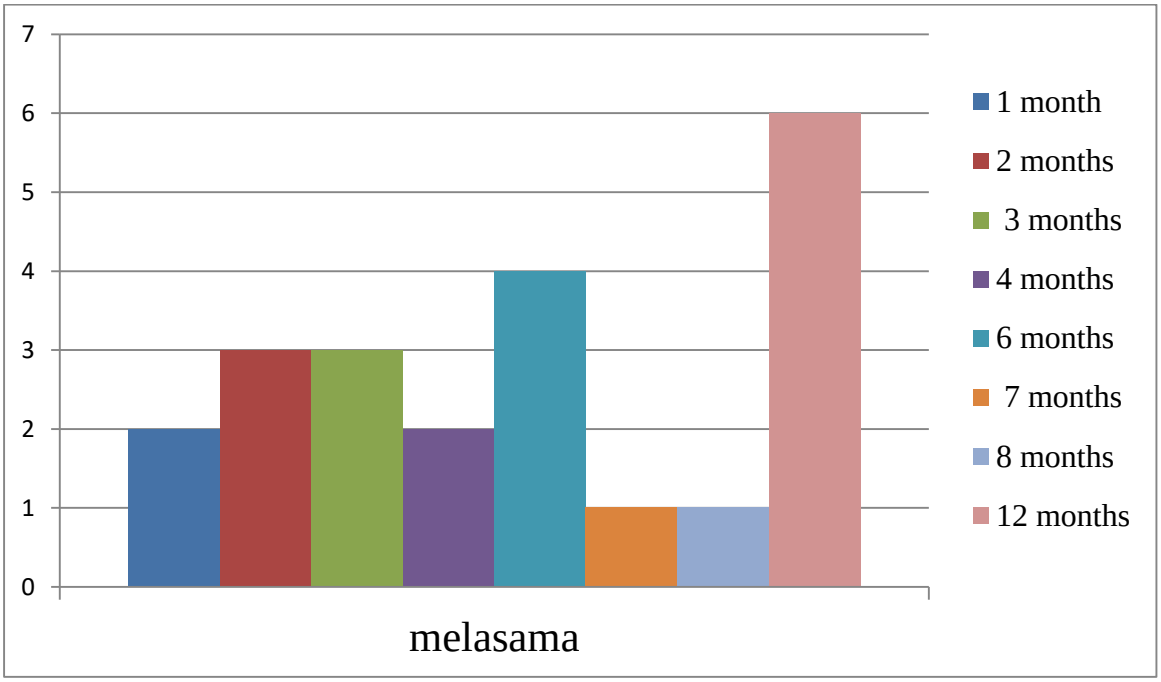


Figure 19

LICHENOID REACTION

Median time of onset - 4months

Time of onset of lichenoid reaction	No of cases
3 months	1
4 months	**1**
5 months	1
Total	**3**

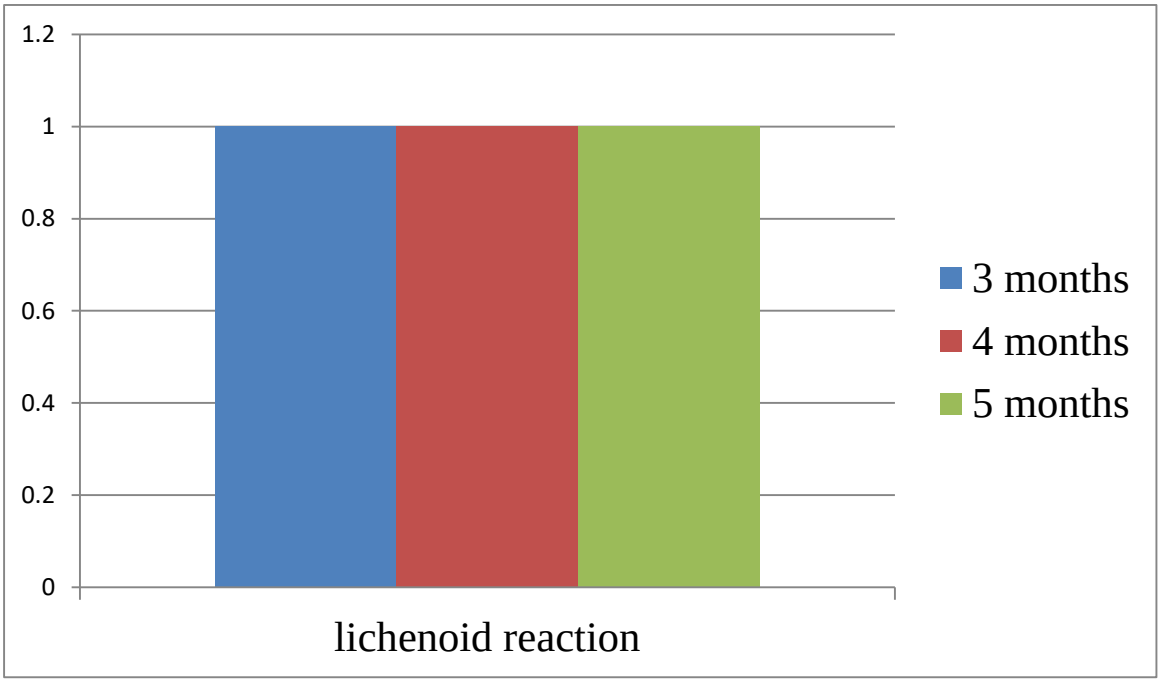


Figure 20

ERYTHRODERMA

Median time of onset - 4 months

Time of onset of erythroderma	No of cases
3 months	1
5 months	1
Total	**2**

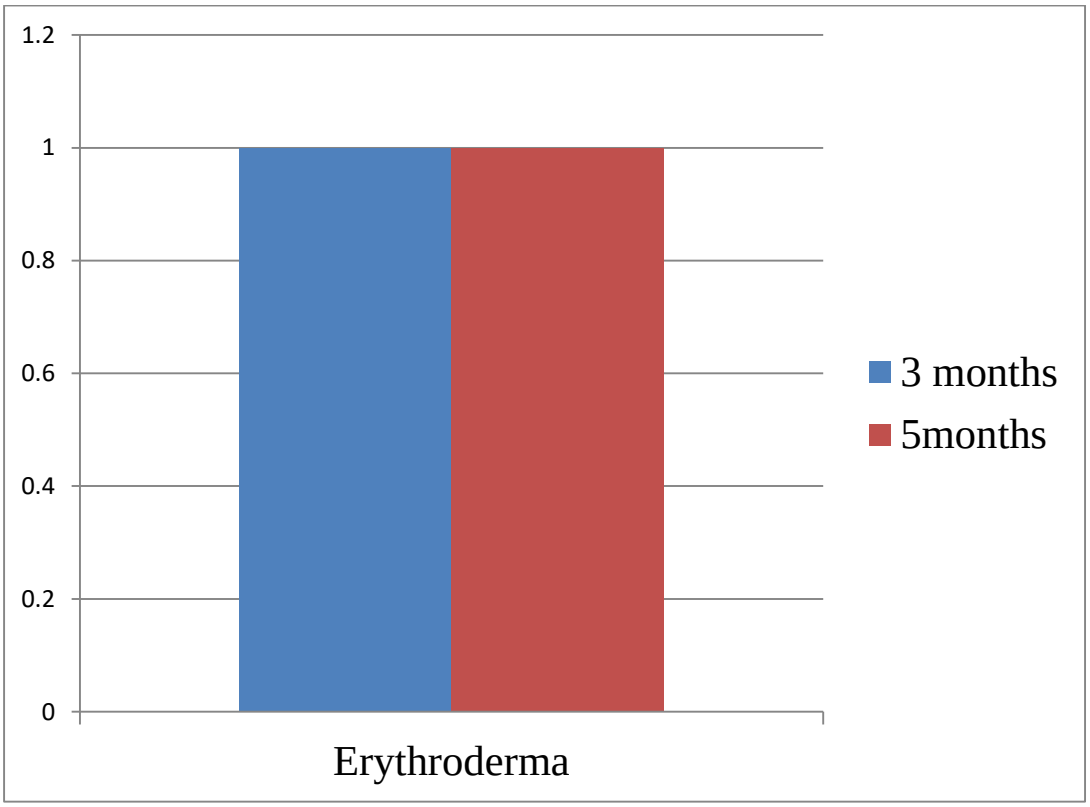


Figure 21

NAIL DYSTROPHY

Median time of onset- 1year

Time of onset of nail dystrophy	No. of cases
1year	2

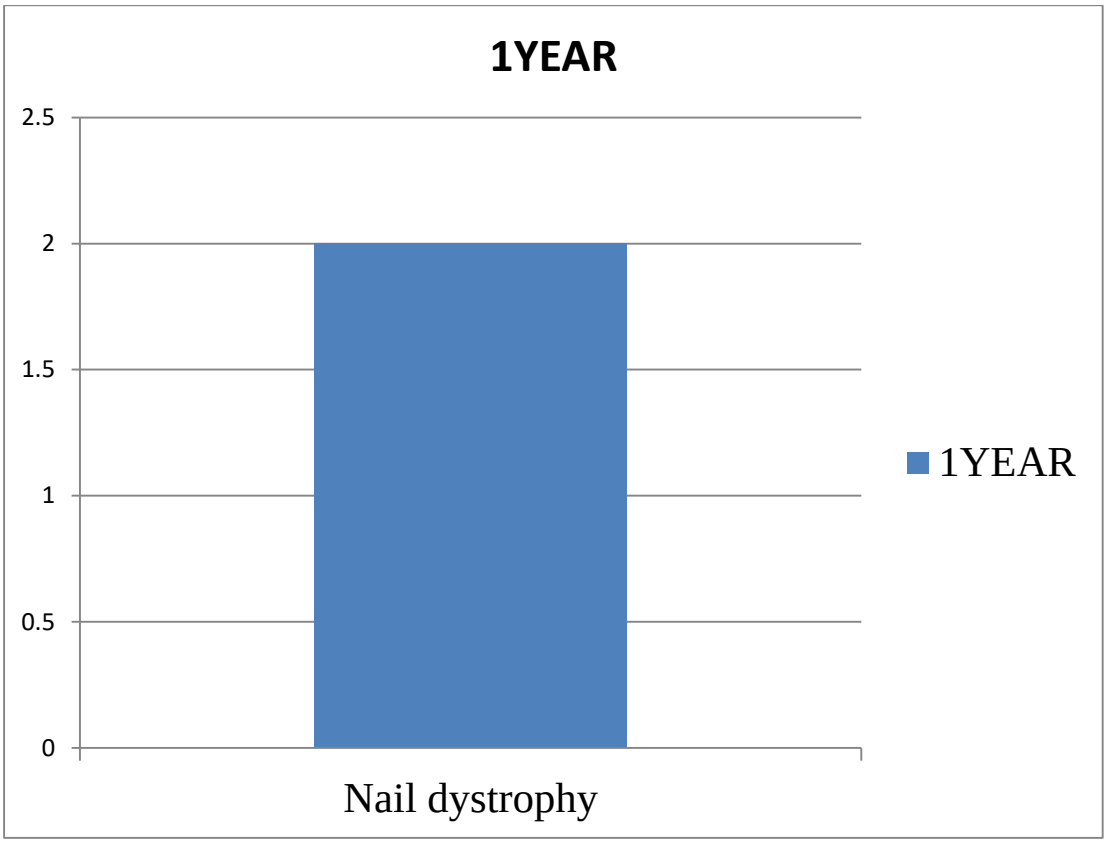


Figure 22

PRURITUS

Median time of onset-3.5 months

Time of onset of pruritis	No of cases
2months	1
5months	1

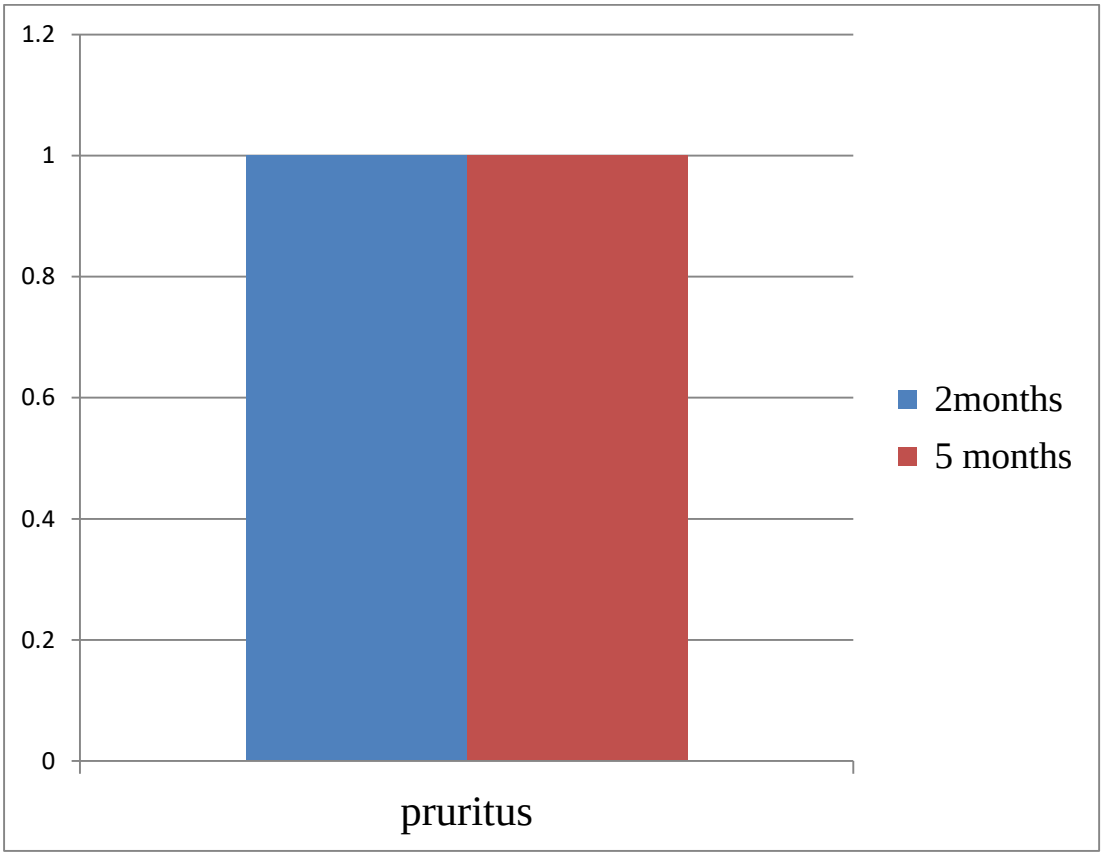


Figure 23

- Median onset of hypopigmentation, lichenoid drug reaction, and erythroderma was 4 months.
- Median onset of melasma like pigmentation was 6 months.
- Median onset of nail dystrophy was 1 year.
- Median onset of pruritis was 3,5 months.
- The earliest side effect observed was pruritis.

DISCUSSION

DISCUSSION

-Sex distribution

The study population consisted of 142 patiens on Imatinib mesylate with 90 males and 52 females.

-Age distribution:

The age of patients varied from 12 to 85 years.56.34% of cases were in age group between 41 and 60;31.69% were in age group between 20 and 40;9.15% were above 60 years of age and 2.82% were less than 20 years of age. The mean age of patient in this study - 44.94%

-Duration of treatment

The duration of treatment of patients in our study ranged from 3 months to 20 years.

-Underlying disease

Out of 142 patients,119 patients were CML and 23 patients were GIST

-Total incidence of CADRs:

Out of total 142 patients on Imatinib mesylate 600mg per day during the study period of 7 months ,55 patents had at least 1 CADRs.

The overall incidence of CADRs in this study was found to be 38.73% which is comparable with that observed in an European study 13.6% by Emine DERVIS1 et al. Out of 119 CML patients 46 (38.66%) patients had atleast one CADRs. Out of 23 GIST patients 9(39.13%) patients had atleast one CADRs.

CADRs were more commonly reported in the age group of 41 to 60 years.

Skin changes

- HYPOPIGMENTION

The commonest CADRs in our study is hypopigmentation and was seen in 23 patients (16.22%) which is lower than a study done by B. Arora, et al where it was 40.9%.The prevalence of hypopigmention in CML patients was 32.94%.The prevalence of hypopigmention in GIST patients was 33.1%. Median time of onset was 4 months which is compared with B. Arora et al study (4weeks) Hypopigmentation was initially more obvious over palms then became genralised in our patients. According to National Cancer Institute Scale Version 4, Which Classifies Severity. Grade 2 hypopigmention was noted in all 23 patiemts >10% of body surface area).

-MELASMA LIKE PIGMENTATION

Melasma like pigmentation was noted in 21 patients (14.81%) which is higher than a study done by B Arora et al where it was 3.6 % but it is lower than Mohammed K. AL – Hattab et al study in which he observed melasma in 19.3%.

Median time of onset was 6 months. The prevalence of Melasma like pigmentation in CML patients was 33.07%. The prevalence of Melasma like pigmentation in GIST patients was 33.7% .Dermal type of Melasma was noted in all patients Woods lamp showed enhancement of pigmentation. Hyperpigmention was seen in cheeks, forehead, bridge of nose, eyebrows. No case of hyperpigmentation of the trunk or extremeties was seen in our patients, although it was reported in Doru T Alexandrehesu et al study where he observed hyperpigmentation on anterior chest and abdomen. The exact pathomechanisms of melasma like pigmentation still remains unclear. It may be due to pigmented breakdown products of the drug itself or drug metabolites chelated with iron.

-LICHENOID DRUG ERUPTION

Lichenoid drug reaction was observed in 3 patients(2.10%) .Fifteen cases were reported in literature .In our study 2 males(1.41%) and 1 female (0.70%) were affected. Median time of onset was 4 months

.In our study skin lesions were noticed over extremities, face, trunk, palms and soles. Skin biopsy showed hyperkeratosis, basal layer degeneration, pigmentary incontinence and perivascular lymphocytic infiltrate.The patients were treated with systemic and topical steroids.

-ERYHTRODERMA

Erythroderma was seen seen in 2 patients (1.40%) which is lower than a study conducted by Emine DERVIS et al(1.5%) .We observed one case in male (0.70%) and one case in female (0.70%). Median time of onset was 4months which is higher than study conducted by Emine DERVIS et al (one patient had erythroderma after three months of imatinib therapy). Biopsy was taken for the patient. The patient were treated with systemic and topical steroids. Lesions started to resolve on follow up and prescribed topical emollients.

-NAIL DYSTROPHY

In our study nail dystrophy was noted in 2 (1.40%) male patients only. One patient had beaus line over both thumb and other patient had dystrophy of all toe nails which is comparable with Deguchi et al. study in which he reported psoriasiform, palmoplantar hyperkeratosis and nail dystrophy after treatment with imatinib in 3 patients with no previous history of psoriasis.

-POMPHOLYX

In our study one male case (0.70%) developed pompholyx which is not reported in earlier studies. It could be an incident association not realted to Imatinib therapy.The patient was treated with topical corticosteroids and the lesion does not recur on continuation of drug.

-NAIL PIGMENTATION

In our study one female case (0.70%) shown nail pigmentation. Prabas et al reported nail pigmentation in his study. In our case diffuse pigmentation of all nails were observed. Toe nails were normal.

PRURITUS

In our study two male patients developed pruritus (1.40%) which is compared with Mohammed K. AL – Hattab et al study where he reported pruritus in 16 patients (1.23%) from 1,305 people. In our study One patients developed itching over extremities and other patient had itching over upper back without any skin lesions.

SUMMARY

SUMMARY

- CML and GIST patients who are all treated with Imatinib mesylate 600mg per day were included in this study
- CML outscored number of GIST patients in our study
- Total number of patients on Imatinib mesylate were 142.
- Males were 90 patients and females were 52 patients
- Total number of patients with CADRs-55
- Total prevalence of CADRs 38.73%
- Total number of males with CADRs 32 (22.53%) and females with CADRs- 23(16.20%)
- The age of patients varied from 12 to 85 years..
- The mean age of patient in this study - 44.94%
- CADRs were more commonly reported in the age group of 41 to 60 years
- The commonest CADRs in our study is hypopigmentation which is seen in 23 patients (16.22%).Initially more obvious over palms and gradually became generalized in distribution.
- Melasma like pigmentation was noted in 21 patients (14.81%).Dermal type of melasma were noted in all patients. Woods lamp showed enhancement of pigmentation.

- Hair changes and mucosal changes were not seen in our study
- Life threatening cutaneous reactions like DRESS, SJS, TEN were not seen in our study .
- Other side effects like psoriasis,pityriasis rosea, acneiform eruption, photosensitivity,erythema nodosum, sweets syndrome was not encounter in our study
- Hence long term follow up will be needed to find out the course of skin changes which occured due to Imatinib and also to find out long term complications.

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PROFORMA

Name:

Age /sex:

Address:

Occupation:

Contact no:

Diagnosis:

Treatment started on:

Duration b/w onset of

treatment & side effects:

HISTORY:

H/o itching

H/o rashes

H/o photosensitivity

H/o erythema

H /o eczematous reaction

H/o pustular eruption

H/o bullous eruption

H/o nodules

H/o icthyosiform lesions

H/o oral ulcers

H/o weight gain

H/o hair fall

H/o increased sweating

H/o pigmentary changes

Skin –

Hair –

Nail –

Teeth –

Mucous membrane –

GENERAL EXAMINATION:

Conscious Orientation

Pallor

Icterus

Pedal edema

Clubbing

Generalized lymphadenopathy

Vitals- BP

Pulse

Temp

OTHER SYSTEM EXAMINATION:

CVS

RS

P/A

CNS

DERMATOLOGICAL EXAMINATION:

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு : புற் றுநோய் மருந்து சிகிச ைசையினால் தோலில் ஏற்படும்

பக்கவில ளவுகள் குறித்த ஆராய்ச்சி .

பெயர்: தேதி:

வயது: உள்நோயாைளி எண்:

பால் : ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களு ம் முழுமையாக எனக்கு விளக்கப்பட்டது.

எனக்கு வி ளக்கபட்ட விஷயங்களும நான் புரிந்து கொண்டு எனது முழுமனதுடன் சம்மதிக்கி றேன் .

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் பசாந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகினறேன் மற்றும ம நான் இந்த ஆராய்ச்சியில் இருந்து எந்த நேரமும் பின்வாங ்காலாம் என்றும் அதனால்எந்த பாதிப்பும் எனக்கு ஏற்படாது என்பதையும் புரிந்து கொண்டேன்.

நான் என்னுலடய சுய நினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் பங்கு கொள் ள சம்மதிக்கிறேன்..

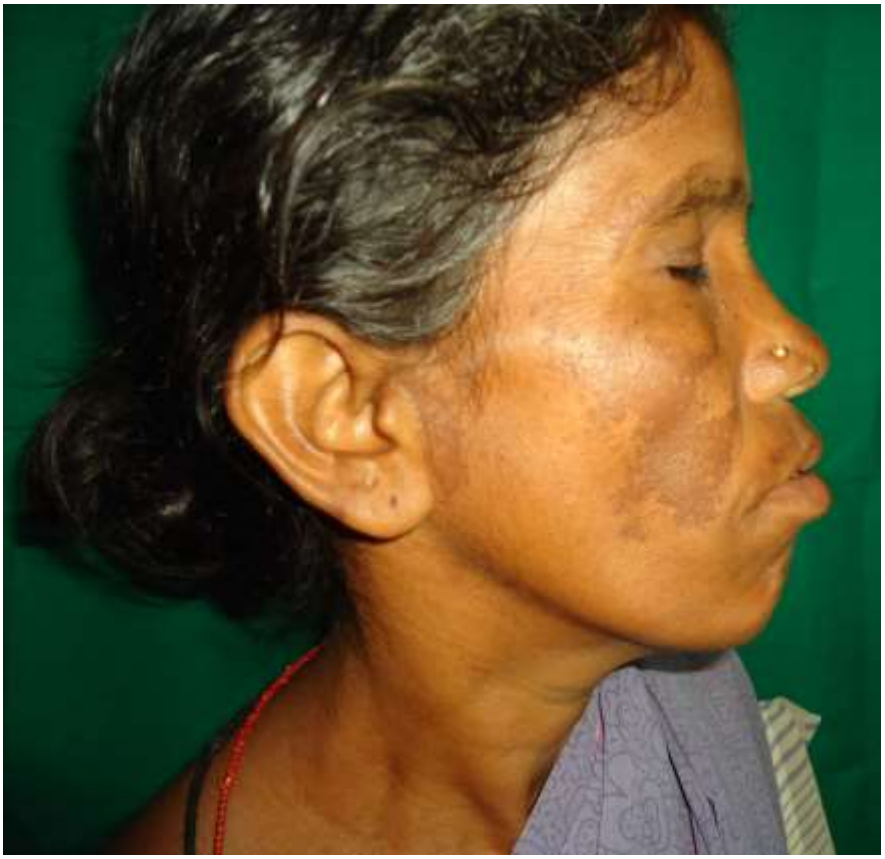
ய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு : புற் றுநோய் மருந்து சிகிச ைசையினால் தோலில் ஏற்படும்

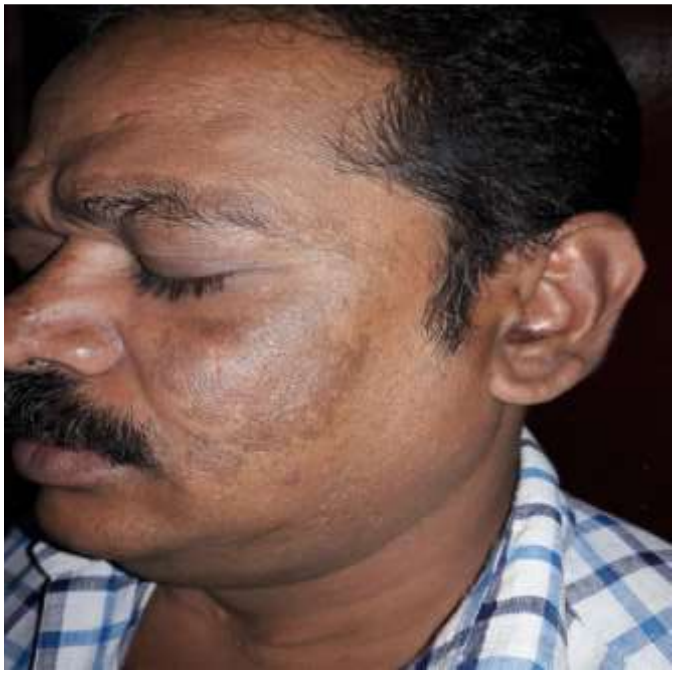
பக்கவில ளவுகள் குறித்த ஆராய்ச்சி .

GENERALISED HYPOPIGMENTATION

MELASMA LIKE PIGMENTATION



MELASMA LIKE PIGMENTATION



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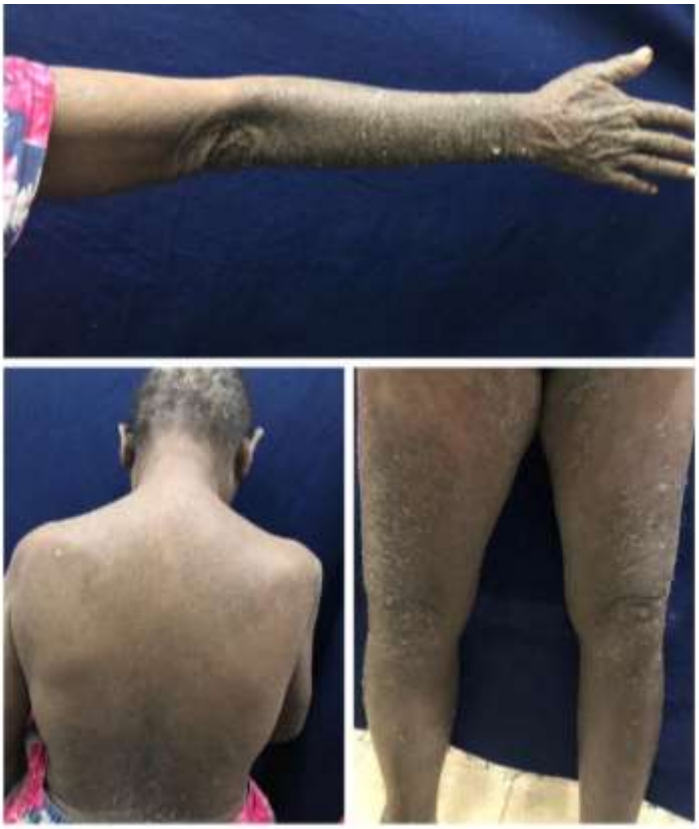
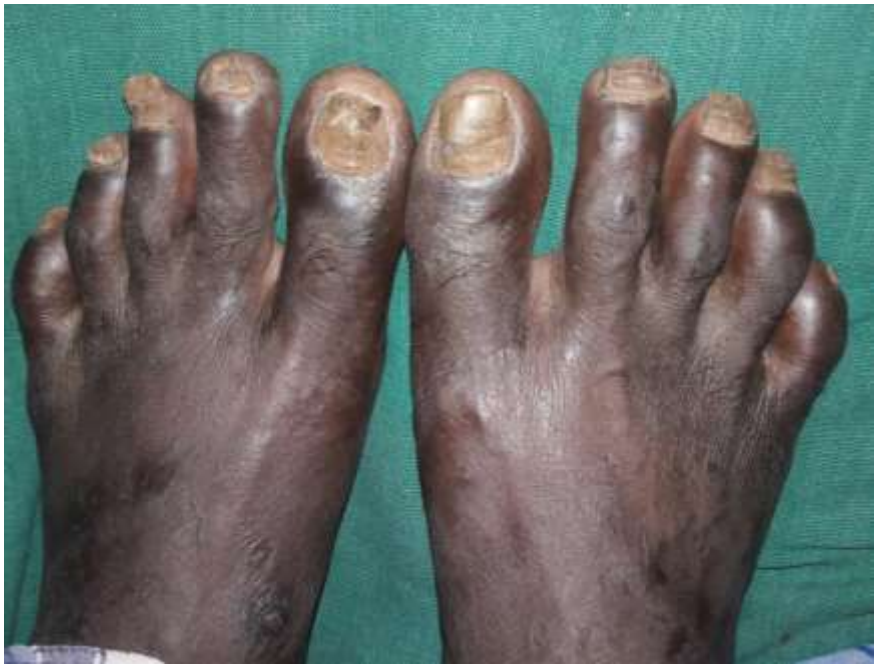
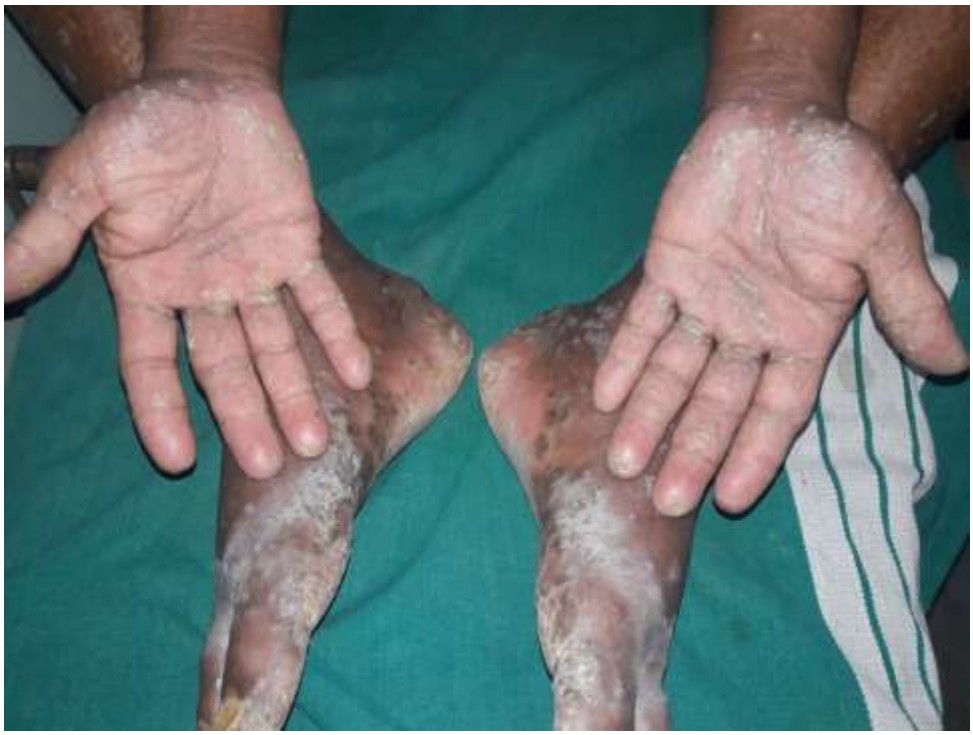


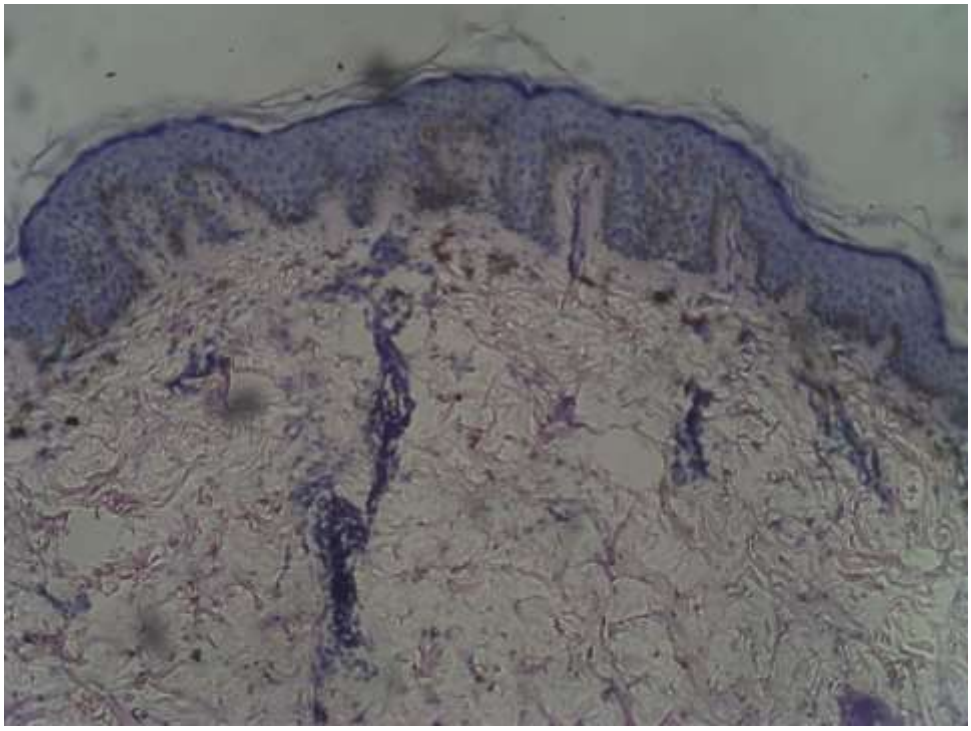
ERYTHRODERMA



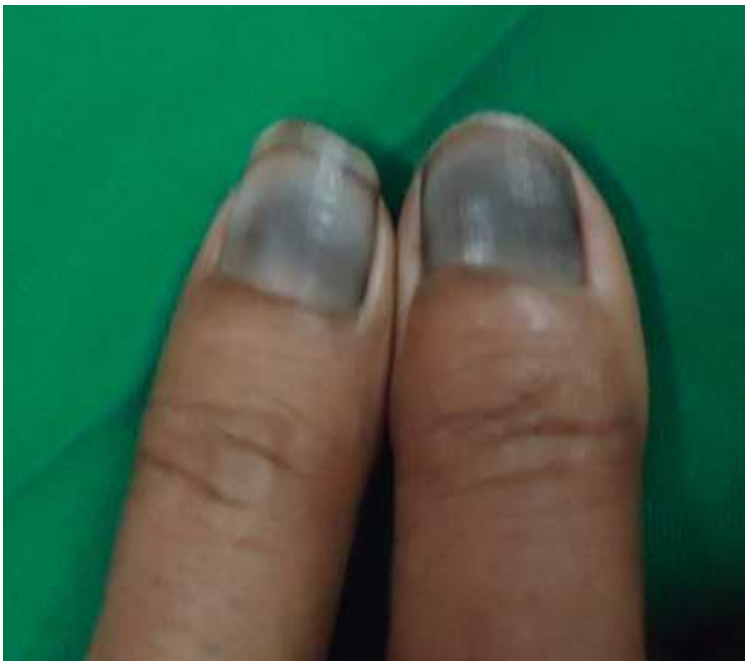
NAIL DYSTROPHY

LICHENOID REACTIONS





Biopsy from Lichenoid papules - Hyperkeratosis, basal layer degeneration, pigmentary incontinence and perivascular lymphocytic infiltrate.



NAIL PIGMENTATION

S. No.	NAME	AGE	SEX	DIAGNOSIS	DOB STARTED	ADVERSE EFFECT	
1	Durgesh	12	M	CML	11-04-2016	Hypopigmentation	3 months
2	Raja prabhu	14	M	CML	22-12-2016	Nil	-
3	Hemanathan	17	M	CML	22-06-2019	Itching	2 months
4	Nalla Mohamed	19	M	CML CP	19-01-2018	No adverse effect	6 months
5	Nandhini	20	F	CML	27-05-2016	Hypopigmentation	6 months
6	Nandhini	20	F	CML	01-04-2017	Nil	-
7	Raja	23	M	CML CP	01-12-2015	Hypopigmentation	5 months
8	Manoj Kumar	24	M	CML	21-11-2017	Hypopigmentation	4 months
9	Ragunath	24	M	GIST	01-05-2017	Hypopigmentation	5 months
10	Deepa Lakshmi	25	F	CML	01-03-2015	Hypopigmentation	6 months
11	Lakshmi Priya	25	F	GIST	20-05-2019	Nil	-
12	Perumal	26	M	CML	17-06-2017	Nil	-
13	Radhika	26	F	CML	05-07-2018	Hypopigmentation	6 months
14	Venkatesan	26	M	CML CP	05-09-2016	Nil	-
15	Shanmugapriya	28	F	CML	10-08-2019	Nil	-
16	Maruthapillai	28	F	CML	06-08-2019	Nil	-
17	Rajathi	28	F	CML	20-08-2019	Nil	-
18	Subramaniyan	29	M	CML	01-08-2019	Nil	-
19	Raja	30	M	CML	14-09-2015	No adverse effect	-
20	Kalaiselvi	30	F	CML	01-02-2014	Nail-pigmentation	6 months
21	Surendran	32	M	CML	17-03-2019	Nil	-
22	Thiyagaran	32	M	CML	08-01-2013	Nil	-
23	Raju	32	M	CML	15-06-2019	Nil	-
24	Ganesan	33	M	CML	22-01-2006	No adverse effect	-
25	Nagalakshmi	33	F	CML	01-12-2014	Hypopigmentation	4 months
26	Kalirajan	33	M	CML	10-09-2018	Nil	-
27	Palani Durai	34	M	CML	26-05-2017	Hypopigmentation	6 months
28	Karthikai sami	34	M	CML CP	01-02-2015	No adverse effect	2 Years
29	Gowandamal	34	F	CML	07-05-2019	Nil	-
30	Saravanan	35	M	CML CP	05-07-2015	Hypopigmentation	2 months
31	Guna	35	M	CML	19-06-2017	No adverse effect	-

32	Veerasolan	35	M	CML	22-05-2014	melasma	6 months
33	Eswari	35	F	CML CP	01-12-2018	Nil	-
34	Kaliyamal	35	F	GIST	22-02-2018	Nil	-
35	Selvi	36	F	CML	01-04-2016	melasma	2 months
36	Karupaiya	36	M	CML CP	03-11-2006	melasma	2 months
37	Adaikalaraj	36	M	CML	15-09-2017	erythroderma	3 months
38	Meena	37	F	CML	01-11-2014	melasma	3 years
39	Murugesan	38	M	CML CP	01-07-2015	No adverse effect	-
40	Sivakumar	38	M	CML	22-10-2015	No adverse effect	2 years
41	Petciyappan	38	M	CML	01-09-2017	Hypopigmentation	2 months
42	Rajammal	38	F	CML	18-05-2019	Nil	-
43	Pandiammal	38	F	GIST	24-08-2019	Nil	-
44	Parasuraman	38	M	CML	13-05-2019	Nil	-
45	Harunrasitha	39	F	CML	07-03-2013	melasma	8 months
46	Rajendran	40	M	CML	01-07-2017	No adverse effect	-
47	Soundarammal	40	F	CML	18-09-2017	No adverse effect	-
48	Karupasamy	40	M	CML	03-08-2017	Hypopigmentation	3 months
49	Ravichandran	40	M	CML	01-10-2017	No adverse effect	-
50	Selvam	41	M	CML	13-02-2019	melasma	1 Year
51	Saroja	42	F	GIST	30-09-2014	Nil	-
52	Selvan	42	M	CML	14-6-2006	No adverse effect	-
53	Nandasamy	42	M	GIST	16-05-2019	Nil	-
54	Ramesh	42	M	CML	15-06-2019	Nil	-
55	Danasekaran	43	M	CML	28-09-2015	No adverse effect	-
56	Muthu Lakshmi	43	F	CML	02-03-2016	melasma	4 months
57	Iruthayaraj	43	M	GIST	18-05-2019	Nil	-
58	Kaliraj	43	M	CML	16-04-2019	Nil	-
59	Arokiya thaya	43	F	CML	17-04-2019	Nil	-
60	SomaSundaram	44	M	CML CP	06-06-2015	Hypopigmentation	4 months
61	Thangaiyah	44	M	CML	09-09-2016	melasma	3 months
62	Sankar Selvan	45	M	CML	01-02-2018	No adverse effect	2 months
63	Mahalakshmi	45	F	GIST	03-01-2018	No adverse effect	-

64	Radha Krishnan	45	M	CML CP	01-06-2017	Hypopigmentation	8 months
65	Rajkumar	45	M	CML	01-07-2013	Nail dystrophy	1 Year
66	Rasu	45	M	CML	13-07-2018	No adverse effect	-
67	Sapani	45	M	CML	17-10-2015	Nil	-
68	Chinna Ponnu	45	F	GIST	10-04-2016	melasma	1 Year
69	Indra	45	F	CML	26-10-2017	Nil	-
70	Murugesan	46	M	CML	01-05-2016	No adverse effect	-
71	Ayyanbose	46	M	CML	16-11-2011	Nil	-
72	Ramar	46	M	CML	01-05-2015	Pompholyx	5 Months
73	Kannammal	47	F	CML	2-3-2015	melasma	6 Months
74	Nallamal	47	M	CML	01-08-2017	melasma	1 Year
75	Chellamal	48	F	CML	20-01-2012	melasma	1 Year
76	Marimuthu	48	M	GIST	22-02-2017	melasma	1 Months
77	Pothum Ponnu	48	F	GIST	04-11-2019	No adverse effect	-
78	Soundaraiyan	48	M	CML CP	29-11-2011	Hypopigmentation	4 Years
79	Therasa	48	F	CML	09-03-2017	Hypopigmentation	4 Months
80	Marimuthu	48	M	GIST	22-02-2017	melasma	1 Months
81	Mariappan	48	M	CML	01-03-2016	Nil	-
82	Arulappan	48	M	GIST	15-08-2016	melasma	3 Months
83	Mariappan	48	M	GIST	17-06-2019	Nil	-
84	Kowsalya	48	F	CML CP	01-10-2015	Nil	-
85	Sundaravalli	48	F	CML CP	01-08-2018	Nil	-
86	Pushpam	48	F	CML	01-09-2017	Nil	-
87	Perumal	48	M	CML	08-09-2017	Nop	-
88	Vanpaye	48	M	CML	24-07-2019	Nil	-
89	Thenmozhi	49	F	GIST	01-12-2016	Hypopigmentation	2 Months
90	Raman	49	M	CML	25-11-2014	Nil	-
91	Eswaran	49	M	CML	01-09-2014	Hypopigmentation	5 Months
92	Murugesan	49	M	CML	03-05-2019		
93	Nisha	50	F	CML	07-07-2018	melasma	1 Year
94	Parameshwaran	50	M	CML	01-04-2017	No adverse effect	2 Years
95	Balu	50	M	CML	15-08-2017	melasma	1 Year, 7 Months

96	Chinappan	50	M	CML	01-03-2016	melasma	6 Months
97	Sakthivel	50	M	CML CP	15-07-2015	Hypopigmentation	1 Year
98	Pitchaimani	50	M	CML	21-03-2016	No adverse effect	6 Months
99	Kondamal	50	F	CML	01-07-2014	melasma	1 Year
100	Thavulath Nisha	50	F	CML	16-07-2019	Nil	-
101	Sivabakiyam	50	F	CML CP	05-07-2015	Lichenoid drug reaction	-
102	Nagaraja	50	M	CML	23-05-2019	Nil	-
103	Sivagnam	50	M	CML	06-07-2019	Nil	-
104	Dhanasekar	51	M	CML	01-04-2012	melasma	3 Months
105	Manoharan	53	M	CML	01-05-2010	Nil	-
106	Malarvizhi	54	F	CML	09-11-2017	Hypopigmentation	2 Months
107	Masanam	54	M	CML	03-06-2017	Nil	-
108	Chinnamal	54	F	CML	03-07-2017	Nil	-
109	Rajkumar	54	M	CML	17-02-2019	Nil	-
110	Eswari	54	F	CML CP	18-04-2019	Nil	-
111	Perumal	54	M	CML	16-08-2014	Nil	-
112	Thangavel	55	M	CML	03-04-2017	melasma	6 Months
113	Sangili	55	M	CML	02-08-2018	Nil	-
114	Mayil	55	M	CML	01-06-2014	Lichenoid reaction	5 Months
115	Nagajothi	55	F	GIST	01-06-2014	Hypopigmentation	10Months
116	Ganesan	56	M	GIST	17-07-2019	No adverse effect	
117	Rajendran	56	M	CML	01-04-2016	No adverse effect	
118	Arul samy	56	M	CML	01-08-2012	Nil	
119	Dharmar	56	M	CML	17-06-2019	Nil	
120	Chelladurai	56	M	CML	10-08-2018	Nil	
121	Panchavarnam	57	F	CML	01-04-2017	Nil	
122	Saraswathi	58	F	GIST	03-09-2015	Hypopigmentation	7 Months
123	Panju	59	F	GIST	11-09-2018	Nil	
124	Ramachandran	59	M	CML	10-09-2019	Nil	
125	Selvi	60	F	GIST	25-05-2016	No adverse effect	1 Year
126	Pappa	60	F	GIST	21-08-2018	Nil	

127	Tamilselvi	60	F	CML	04-02-2019	Hypopigmentation	6 Months
128	Tamilselvi	60	F	CML	16-03-2019	Nil	
129	Thangavel	60	M	CML	18-04-2019	Lichenoid drug reaction	4 Months
130	Vijaya Raman	62	M	CML	26-05-2014	No adverse effect	3 Years
131	Manoharan	62	M	CML	11-04-2015	Nil	-
132	Vasuki	63	F	CML	31-10-2018	Nil	
133	Mariyammal	63	F	CML	01-12-2018	Erythroderma	5 Months
134	Murugesan	64	M	CML	27-12-2016	No adverse effect	
135	Pitchaimani	64	M	CML	01-08-2018	Nil	
136	Kesavan	65	M	GIST	01-02-2013	Nil	
137	Kanpasam	65	M	CML	02-07-2019	Nil	
138	Ayyavu	68	M	CML	03-08-2019	Nil	
139	Thangavel	70	M	GIST	01-03-2018	Itching	5 Months
140	Sundaraya	75	M	CML	02-08-2018	No adverse effect	
141	Mariammal	75	F	CML	17-09-2019	melasma	4 months
142	Periyammal	85	F	CML	07-02-2018	Nil	
TOTAL							
			MALE	90			
			FEMALE	52			

URKUND

Urkund Analysis Result

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Significance: 17 %

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https://academic.oup.com/annonc/article/15/2/358/155157
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23

ANTI PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled, entitled "**A STUDY ON CUTANEOUS ADVERSE DRUG REACTIONS TO IMATINIB"** submitted by **Dr.S. SARANYA** with registration number **201730103** for the award of **MASTER DEGREE** in the branch of **DERMATOLOGY, VENEREOLOGY & LEPROSY** has been personally verified by me in urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 17% percentage of plagiarism in the dissertation.

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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.Saranya
Course	:	PG in MD., DVL
Course of Study	:	2017-2020
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A study on cutaneous adverse reactions to Imatinib
Ethical Committee as on	:	11.02.2019

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary

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