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CONTENTS

Artificial intelligence & machine learning in clinical chemistry: a revolution

After the initial conceptualization of artificial intelligence (AI) in mid 20thCentury, its applications were first utilized for solving the biomedical problems in 1970s only. Machine learning (ML) is one of the core branches of AI which involves converting data from multiple sources into computer augmented and wisdom that imitates human intelligence and helps making predictions or taking decisions.[1] The current trends in health care demonstrate a shift from the heuristic approach to a patient centric evidence based approach. The aim is to make it possible for health professionals to diagnose diseases early, institute treatment and enable predictive, preventive, personalized and participatory medicine for the patients.[2] Bringing together the clinical and laboratory data to improve patient outcome, undoubtedly, is valuable at all levels. We are right on the verge of this major transformation of use of AI in medicine.

In this new AI-supported era, clinical laboratories are moving towards a more specialized role in management of clinical information and quality control, using algorithms and statistical models to perform a specific task effectively without instructions, relying on patterns and inferences. The abundance of health data is slowly leading to a shift from analytical competence in diagnostic tests to the ability to integrate data and simultaneously interpret them within the clinical context with the help of ML.[3] ML could be valuable in defining the accuracy of test, positive and negative predictive values, assist interpretation of the results in the post-analytic phase and ordering the tests automatically. ML makes it possible to detect multiple subtle changes in a profile of multiple analytes within a sample that would otherwise go unnoticed. Many ML generated algorithms provide personalized information to the person.[4] This information ranges from personalized health-related applications for nutrition, physical activity, ovulation cycles, to detection of potassium disorders by use of a built-in electrocardiogram sensor, glucose sensors for monitoring blood sugar etc. It is foreseeable that more such sensors will be used for managing diseases that earlier relied on analysis in lab. This advancement shall also integrate the genomic data, the electronic medical data, the clinical symptomatology using computational analysis for the precise decision making regarding the individualized treatment for various diseases required as per pharmacogenomics of an individual.[5]

Besides this, there may be challenges posed due to issues related to calibration, lot number of reagents or the measuring component producing shifts impairing the ability of algorithm to detect error. Finally, to ensure that the algorithms continue to function as intended after the initial development/ implementation phase, structured evaluation protocols and quality-control measures for these algorithms need to be developed. More close collaboration amongst the laboratory professionals is needed to provide larger data sets and validation studies to improve ML algorithms. ML may also alter the human interaction with humans and machine. Care needs to be taken to ensure that the tools enhance the human healthcare experience and not replace the humanity aspect that underpins clinical medicine. Misinterpretation and automation bias need to be avoided. In this direction *clinlabomics* is the newly proposed concept.[6] Data security and reliability should be evaluated and regularly updated. Also, the privacy of patients is an

important concern. Data sharing of an individual may be forced. So many such ethical issues need to be sorted. Guidelines to get access to data need to be developed as there can be obstacles in aggregating the data existing in silos. Interdisciplinary approach between the medical and engineering experts is the need of the hour to upgrade curriculum and joining hands in research to address the future challenges of AI.

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Globesity : the global obesity epidemic

As we are emerging out of Covid -19 epidemic after more than 2 years, our attention is getting drawn towards another previously running crisis of global obesity which has reached its all time high, thanks to the specialized life style which Covid-19 pandemic brought as a freebie and which costed us exorbitantly, both mentally and physically.

According to World Health Organization (WHO) estimates, the overall burden of obesity has nearly tripled in last 50 years. More than 1 billion people worldwide are obese – 650 million adults, 340 million adolescents and 39 million children. The number is ever increasing and globally almost 5 million people are added as new obese population every year. WHO estimates that by 2025, approximately 167 million people – adults and children – will become less healthy because they are overweight or obese. We have already learned lessons of higher risk of disease and death in obese while handling Covid-19 pandemic. On the occasion of World Obesity Day, 4 March 2022 WHO urged the countries to do more to reverse this predictable and preventable health crisis of globesity with a caption theme : *Accelerating action to stop obesity*. World Obesity Day returns on 4 March 2023 with the new theme : *Changing Perspectives: Let's Talk About Obesity.*

Obesity is a lifestyle disease with a great familial propensity . Increased intake of high energy yielding foods , lack of physical activity, sedentary life style , rise in alcoholism ,easy availability of quick modes of transport and several other factors contribute significantly to risk of getting obese. It is a disease impacting most body systems including heart, liver, kidneys, joints, and reproductive system. It leads to a range of noncommunicable diseases, such as type 2 diabetes, cardiovascular disease, hypertension and stroke, various forms of cancer, as well as mental health issues. People with obesity are also three times more likely to be hospitalized for COVID-19. The economic burdens of obesity are difficult to estimate and may be causing reasonable cost to the national budgets of every country affected with obesity.[1]

WHO defines overweight and obesity as follows:[2]

For Adults:

a) Overweight is a BMI greater than or equal to 25

b) Obesity is a BMI greater than or equal to 30.

For children under 5 years of age:

a) Overweight is weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median

b) Obesity is weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median.

Children aged between 5–19 years :

a) Overweight is BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; and

b) Obesity is greater than 2 standard deviations above the WHO Growth Reference median.

The first step towards prevention and cure is to realize the global prescence of obesity and its impact on the health of an individual and society at large. Obesity is best prevented than treated, the concept in prevention is to act early in life, ideally even before a baby is conceived by ideal nutrition in pregnancy, followed by exclusive breastfeeding upto the age of 6 months and continuing breastfeeding upto 2 years and beyond. [3-5] Effective steps include restricting the marketing to children of food and drinks high in fats, sugar and salt, taxing sugary drinks, and providing better access to affordable, healthy food etc. Urban areas need to design areas for safe walking, cycling, and recreation, and schools need to help households teach children healthy habits. In summary, limit energy intake from total fats and sugars, increase consumption of fruit and vegetables, as well as legumes, whole grains and nuts and engage in regular physical activity.[6]

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Factors associated with preference for treatment setting in patients with opioid dependence syndrome

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ABSTRACT

Background: The preference for seeking treatment from a particular setting depends upon various socio-demographic and clinical variables of patients with opioid dependence syndrome. **Aims:** To assess the factors associated with preference for treatment setting in patients with opioid dependence syndrome. It is being hypothesized that de-addiction clinic (DAC) patients would prefer deemed services and community psychiatry services(CPS) patients would prefer service close to their homes. **Method:** It is an observational, interventional and cross-sectional study. A total of 100 consecutive male patients with opioid dependence syndrome (ODS) as per ICD-10, enrolled from DAC and CPS of tertiary care teaching hospital of North India. Socio-demographic and clinical details gathered on semi-structured proforma and reasons for seeking treatment from particular setup. **Results:** Forty eight percent of DAC patients were educated up to 10th standard while 46% of CPS treatment setting patients are primary passed only (p = 0.032) and 54% of DAC patients have income less than 25000/- INR per month while 94% of CPC patients have monthly income less than 25000/- INR (p = 0.000). Majority of DAC patients (74%) hailed from Punjab while 60% of CPS patients were from Chandigarh (p = 0.001). Majority of DAC patients (54%) were using semi-synthetic form of opioid while 44% of CPS sample used the natural form of opioid (p = 0.022). **Conclusion:** This study found out that DAC is preferred due to deemed services while CPS setup were visited by ODS patients due to proximity of the facility to their home. While DAC is visited by ODS patients due to financial reasons to quit the drug while CPS is visited due to health related reasons due to opioid.

Key words: Opioid dependence, treatment preference, de-addiction, community.

INTRODUCTION

India has significant problem of opioid abuse disorder and has the high prevalence of illicit opioid consumption. According to the study by Chavan et al, which represents the data from the state of Punjab under the National Mental Health Survey 2016, the prevalence of other substance use disorder (including opioid but other than alcohol and tobacco) is 2.48%.[1] Among the factors determining the treatment seeking behavior of patients; socio-demographic and clinical profile have been studied in camp approach for treatment of drug dependence by Indian study.[2] Various other factors like education status, employment status, duration of dependence, psychiatric co-morbidity have been compared in patients visiting a de-addiction camp to those being treated in inpatient hospital setup and reported that patients treated at camp are older, less educated, have longer duration

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of dependence and using mainly natural opioids and alcohol. [3]

According to the Punjab opioid dependence survey, demographic profile of opioid users is varied as : 99% males, 89% educated, 54% married and 83% being employed. However the drug use profile shows most common opioid being heroin (53%).[4] Dehradun based study showed a relatively higher rate of prevalence of substance abuse with increasing literacy status among school going adolescents, who hail from economically stable families with good familial relationship. The company of peer group and pocket money provided by family, makes the person prone to the habit of substance abuse. [5]

Another study from AIIMS, New Delhi community clinic of Sunder Nagari found out that opioid−dependent patients seeking treatment were mostly males with 63% belonging to the age group of 18–35 years, considerable proportion are illiterate (33%) and unemployed (42%) and most of them are married. Most are chronic opioid users with the mean duration of opioid use of around 11 years. Heroin is the primary substance of abuse in this group and is used both by chasing as well as injecting. [6] Another study from the North Indian state of Kashmir, reported that patients with polysubstance abuse preferred to seek treatment from tertiary care de-addiction centre.[7] According to another study on adolescents seeking treatment from tertiary care de-addiction facility reported that majority of the them are using alcohol, opioids, tobacco and cannabis and are from joint families and having good social support.[8] Arun et al mentioned reasons like wish to improve one's health as the most common reason for seeking treatment, while other reasons for treatment seeking are awareness and easy availability of treatment facility, internal motivation amongst substance abusing patients seeking treatment from community clinic.[9]

Amongst alcohol and drug dependent patients; reasons for not seeking treatment from hospital based de-addiction service included a lot of time being wasted in seeing a doctor, structured and rigid programme of hospital being very difficult to fit in, uncooperative and discriminatory attitude of staff members, high cost of treatment and inadequate transport facilities. Whereas the community outreach services are more acceptable, affordable, cost effective, and conducive for health education and group interaction, strong influence of family and community leaders.[10]

However, there are no studies on factors determining preference to seek treatment from particular treatment setting in patients with substance use disorders especially opioid dependence. Neither it is known that some socio-demographic, behavioural, service provider related and other clinical factors may influence the choice of a patient to seek treatment from particular place or setting. The present study was planned to explore such factors influencing treatment seeking behaviour .

MATERIAL AND METHODS

A total of 100 consecutive male patients (age 18-60 years), attending the outpatient department of tertiary care de-addiction clinic (DAC) and community psychiatry services (CPS) for first time and diagnosed with opioid dependence syndrome (ODS) as per ICD 10 diagnostic criteria were inducted.[11] Patients with co-morbid dependence on other substances except nicotine and caffeine, neurologically impaired, patients with active symptoms of psychotic illness, intoxicated patients and those not accompanied by reliable informant were excluded. A detailed socio-demographic and

clinical information was recorded on semi-structured proforma which included age, gender, income, education, occupation, family type, religion , residence and type, amount, frequency and duration of opioid use and dependence, money spent on opioid. Principal investigator interviewed opioid dependence syndrome patients in both the settings and the patients were asked to cite the reasons for seeking treatment and preference for particular setting i.e. either DAC or CPS. They were further asked to cite the personal, family related and social/legal reasons for preferring to seek treatment from particular setting. Additionally, Addiction Severity index (ASI) 5th Edition and SOCRATES-8D were administered to assess severity of addiction and motivation for treatment respectively. ASI is a clinician administered scale which taps severity of problem on 0-9 scale under seven domains, takes around 15-20 minutes to administer. Similarly, SOCRATES 8D is used to assess motivation on three domains in drug using individual, administered over 10-15 minutes by the clinician.

Since no objective tool is available to assess the factors associated with preference of treatment setting in opioid dependence patients, hence other co-investigator with considerable years of experience in field of alcohol and drug abuse prepared a questionnaire to elicit the responses, which was first validated in pilot study on 5 patients of ODS and additional responses were gathered and were incorporated into the final questionnaire and applied on rest of the 95 patients.

The study was approved by institutional research and ethics committee and was registered with Clinical Trial Registry of India (CTRI).

Statistical Analysis

Data was analyzed using licensed SPSS software (IBM SPSS Statistics for windows, Version 16.0, Armonk, NY).[12] The Kolmogorov-Smirnov test (Lilliefors Significance Criterion) was used to determine the normality of the data. Categorical data was presented in numbers, percentage while continuous data as mean and standard deviation. Chi square test was used to compare the socio-demographic, clinical profile of patients of both the groups. P-value of less than 0.05 has been considered as statistically significant, 0.000 considered as highly significant.

RESULTS

Socio-demographic and clinical details of DAC and CPS groups:

Out of 100 patients enrolled , 50 each belonged to DAC and CPS group. Patients from both the treatment settings were comparable on mean age (29.94 ± 8.89 in DAC group, 32.38 ± 9.94 in CPS group, p 0.582), marital status, occupation, religion, family type and locality. However, patients reporting to CPS had lower income (p 0.000) ; lower education (p 0.032) and majority were from North Indian tertiary care hospital (p 0.001) (site of study).

On the clinical profile of patients of opioid dependence syndrome, statistically significant results were found on type of opioid used and past treatment history. Patients at DAC were using semisynthetic form of opioid predominately, while at CPS were using natural form of opioid (0.022*). Past history of treatment was present in 42% of DAC patients as compared to a meager 22% CPS sample(p-value – 0.032*).

Table 1: Reasons for preference of treatment setting

S. No.	Service related Reasons	DAC (n=50,%)	CPS (n=50,%)	χ^2(df)	p-value
1.	Is it due to deemed services/expertise of the doctors?	25(50%)	0	3.778(4)	0.437
2.	Did you come to know about the services from other patients?	17(34%)	11(22%)		
3.	Is it due to Indoor facility being available?	2(4%)	0		
4.	Is the service close to your home?	0	32(64%)		
5.	Are you already in treatment with other department of the hospital?	1(2%)	0		
6.	Were you referred from the other departments of the hospital/ dispensary?	5(10%)	0		
7.	Due to availability of Doctor, staff and registration under one roof?	0	3(6%)		
8.	Is the service less time consuming and easy to follow up?	0	2(4%)		
9.	Is it due to availability of free medication?	0	2(4%)		

Table 2 : Personal reasons cited by the patients at two treatment settings

S. No.	Personal Reasons	DAC (n=50,%)	CPS (n=50,%)	χ^2(df)	P-Value
1.	Are you seeking help for health related issues(weakness/decreased libido/ thrombophlebitis/ deep vein thrombosis/comorbid psychiatric medical illness)?	8(16%)	24(48%)	18.552 (6)	0.005*
2.	Are you seeking help for Substance related issues (body ache/ lacrimation/nasal discharge/ piloerection/ hot-cold flushes/ sleep disturbance)?	6(12%)	8(16%)		
3.	Are you seeking help due to financial reasons (increasing cost of drugs/ decreased income on account of absenteeism from work)?	22(44%)	8(16%)		
4.	Are you seeking help due to occupational reasons (unemployed/decreased reputation at workplace/decreased output/ absenteeism)?	5(10%)	1(2%)		
5.	Are you seeking help due to Health care system related reasons (easy accessibility/ free treatment/ counseling facility)?	1(2%)	0		
6.	Is it that you are strongly motivated to finally quit on drugs?	7(14%)	8(16%)		
7.	Is it due to thinking of future (dark/ lonely/ outcasted)?	1(2%)	1(2%)		

^{NS}p= not significant, * p <0.05 significant, χ^2 - chi -square, df – degree of freedom

Table 2 depicts the personal reasons for seeking treatment. Increasing cost of the drug and decreased income on account of absenteeism from work has been the predominant reason cited by the DAC attending patients (44%) as compared with CPS patients who attended the community clinic due to health related issues primarily (48%) (p-value = 0.005*)

Table 3: Family related reasons for preference of seeking treatment from DAC and CPS

S. No.	Family reasons	DAC (n=50, %)	CPS (n=50,%)	χ^2(df)	p-value
1.	Are you seeking help due to family financial reasons–(no support from family/ money exhausted in drugs how will materialize marriage of children tomorrow/ financial crisis)?	6(12%)	23(46%)	22.196# (5)	0.000**
2.	Are you seeking help due to poor IPR issues (regular conflicts with spouse or parent/ spouse left/ filed divorce)?	27(54%)	8(16%)		
3.	Are you seeking help due to parental pressure (fear of disclosure to family members/ scold/ neglect/ abuse/aggression/24 hour vigilance by family members/ disowned from property)?	5(10%)	5(10%)		
4.	Are you seeking help due to your children (commitment to children/behavior issues by children-disobey/disrespect/ aggression)?	7(14%)	9(18%)		
5.	Are you seeking help due to your relatives taunt/laugh at you?	4(8%)	2(4%)		
6.	Are you seeking help due to religious reasons?	1(2%)	3(6%)		

NS p= not significant, *significant, ** highly significant , χ - chi-square, df – degree of freedom, # Yates correction

As per table 3, amongst the family reasons for seeking treatment from a particular setting, DAC sample (54%)reported IPR issues as the most problematic reason forcing them to seek treatment compared with 16% of the CPS sample. While CPS sample (46%) quoted familial financial crisis due to opioid use as the foremost reason for seeking treatment in contrast to 12% of the DAC sample and which is highly significant statistically.(p-value = 0.000**)

Preference for particular setting with severity profile on Addiction Severity Index :

In the index study, Addiction severity index(ASI)[15] found out high severity in family/social domain in DAC patients which corroborates with the findings on reasons for preference for treatment setting questionnaire, in which 54% DAC patients reported problematic family reasons like poor IPR for seeking treatment. DAC sample reported less severity in employment, medical and alcohol domain as CPS sample($p<0.05$*).

Preference for particular setting on SOCRATES-8D scores :

Motivation of patients assessed on SOCRATES 8D[16], approximately half of the patients highly recognized the problem in both the setup. But more of CPS patients(84%) were low and very low

Table 4 : Social/Legal Reasons for preference of seeking treatment from DAC and CPS

S.No.	Reason	DAC (n=50,%)	CPS (n=50,%)	χ^2(df)	p-value
1.	Are you seeking treatment due to legal reasons (stringent law/ unable to get drug/arrest/legal proceedings/accidents)?	1(2%)	7(14%)	3.938 (1)	0.047*
2.	Are you seeking treatment due to social reasons (Marginalised / neglected/ derogatory comments/ disrespected)?	1(2%)	0		
3.	Not applicable	48(96%)	43(86%)		

NS p= not significant, *significant , χ - chi-square, df – degree of freedom, # fisher exact test

Table 4 shows that stringent law and being marginalized by society was cited as the reason for attending DAC cited by 4% as compared with stringent law only as the reason for treatment seeking by 14% of the CPS attending patients.(p-value = 0.047*)

on ambivalence as compared with only 62% of the DAC patients . 82% of CPS patients were high to very high in taking steps as compared to 64% of DAC patients.

DISCUSSION

Index study was conducted to explore the factors associated with preference for treatment setting in patients with ODS seeking treatment at DAC and CPS of GMCH Chandigarh.

Patients of ODS with urban background, married, employed, using heroin, relatively poor motivation prefers DAC setting and same has been seen in other studies too.[8,9,10]Patients with educational status matriculation and above preferred DAC while those educated up to primary/middle preferred CPS setting in index study finding. As far as occupation is concerned, drivers specifically preferred DAC setting whereas farmers utilised CPS mostly. However, authors could not find any literature to support these findings. Type of opioid is taken into account then semisynthetic users preferred DAC services in contrast to natural opioid users who preferred community clinic services and which has been reported in earlier study from the same centre.[3]DAC setting was the preferred choice in ODS patients with past history of treatment, while treatment naive preferred community clinic. Amongst the DAC attending patients, half of the patients answered that they preferred the DAC setup due to deemed services while nearly 2/3rd of CPS attending patients preferred the set-up due to proximity of the services to their residential place. The patients who preferred to visit DAC, cited that increasing cost of the drug and salary deductions due to absenteeism from work(44%) are the personal reasons for choosing DAC service, though the investigator could not find similar study in opioid use, however, a study on alcohol use disorder (AUD) found similar findings of absenteeism from work due to AUD.[13] However, those preferred to attend CPS, cited health related reasons for seeking treatment (48%). While, the

family reasons for preferring treatment setting amongst DAC attending patients was poor interpersonal relationship with family members on account of drug(54%), which are consistent with finding of another study on alcohol use disorder.[14]

Although the study was conducted in a real clinical setting and a questionnaire was developed to elicit responses on various domains regarding preference of treatment setting but has few limitations in the form of small sample size, only male patients being included, and under intoxication patients not being included.

In nutshell we can say that DAC setting is preferred choice amongst atleast matriculated and higher educated ODS patients, drivers, semisynthetic opioid users, and those who seek treatment owing to deemed service and secondary to financial constraints. Patients with ODS who are educated up to primary level only, farmer by occupation, use natural form of opioid with no past history of treatment and proximity of treatment facility to their residential place prefer to seek treatment from CPS setting.

CONCLUSION

It can be concluded from the current study that there are various service related, personal, family, social/legal reasons which are associated with preference for particular treatment setting in relation to socio-demographic and clinical profile of patients with opioid dependence syndrome.

Index study adds to the literature about factors previously unknown about the treatment setting preference in opioid dependence syndrome patients and serves as lighthouse for improvising the existing services.

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D-Dimer: a friend or a foe?

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Haemostasis under normal physiological conditions ensures the smooth blood flow including prevention of blood loss (prothrombotic) and maintains the fluid state (antithrombotic) processes. The whole process is well coordinated and regulated to maintain this delicate balance. The various components include blood vessels and endothelial cells, platelets, coagulation factors, coagulation inhibitors and a special process for clot dissolution or fibrinolysis.

After injury the coagulation cascade rapidly amplifies the generation of thrombin. Thrombin is the central player affecting many processes. Thrombin converts fibrinogen to an insoluble polymer fibrin (a tripod like structure with central E domain and two D-domains). Initially the plasma remains fluid but soon converts to a gel formation as the fibrin polymerizes. Platelets get enmeshed and aggregate in the fibrin as it gels and later form a stable fibrin clot.

Fibrinolysis is required after plug formation to make the vessel patent and resume blood flow. The fibrin clot that was formed needs to be removed by proteolytic enzymes for resumption of blood flow. Tissue injury also activates the proteolytic enzymes tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Endothelium stores t-PA and on injury the t-PA gets released and acts on plasminogen. Plasmin then degrades the polymerized fibrin into multiple varying molecular weight fragments.

This occurs in a stepwise manner where first the fibrinogen, a soluble plasma glycoprotein, is cleaved by thrombin to form fibrin monomers. Next these monomers bind to form double layered thick protofibrills and are held together at the intermolecular D-domain and D-E domains. As the fibrin monomers are polymerizing to form fibrin polymer, thrombin activates Factor XIII to Factor XIIIa, which then acts on the fibrin polymers and attaches the D-D domains covalently, converting the soluble fibrin to an insoluble highly adhesive molecule which stabilises the clot formation plug. The loose fibrin meshwork is acted upon by activated factor XIII, which crosslinks the D-domains present in the adjacent fibrin monomers to form a stable fibrin clot. Meanwhile the plasminogen gets activated by tissue-type plasmongen activator (tPA) or urokinase-type plasminogen activator (uPA) to plasmin. The plasmin cleaves both soluble and insoluble fibrin polymers and releases the D-dimer antigen. Fibrinolysis system gets activated and the plasmin breaks the cross-linked fibrin into DD fragment and E fragment.[1]Thus, multiple varying molecular weight degradation products are produced.

Plasmin degrades both fibrin and fibrinogen, however the adjacent D-domains (D-dimers) are specific to fibrin degradation products, the neo-

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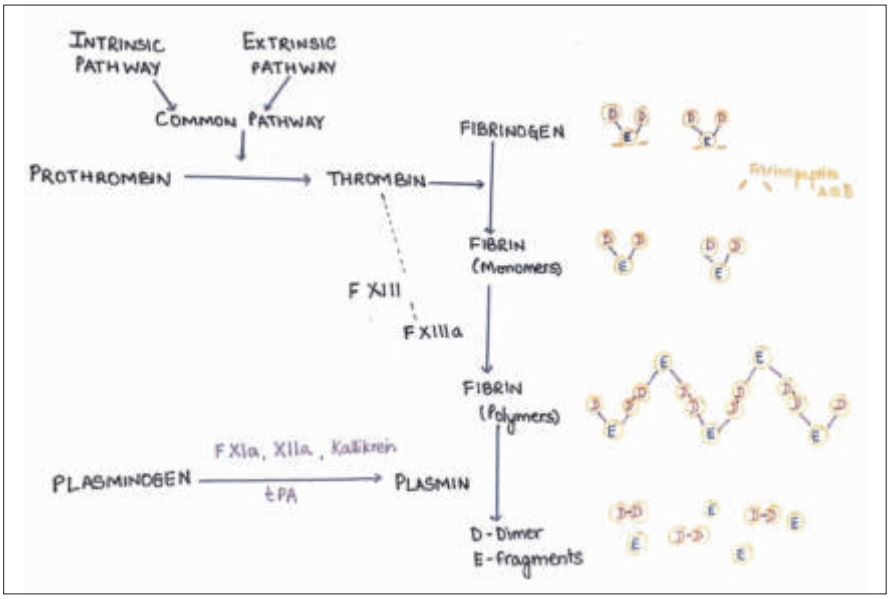

Fig.1: Schematic diagram of coagulation system& D- dimer formation

epitope is a common target for reagent antibodies assessed in the coagulation laboratories and is used as a marker for coagulation and fibrinolytic activity.[2] Practically D-dimer is suggestive of thrombus formation and indicative of action of thrombin, Factor XIIIa and plasmin. Therefore, it's an indirect marker of thrombotic activity.

Laboratory testing:

Samples:

The sample should be collected in a minimum traumatic venepuncture with a wide bore needle avoiding many manipulations which could cause haemolysis. Anticoagulant used is 3.2% buffered sodium citrate in a 9:1 ratio (9 parts blood and one part anticoagulant). This vaccutainer is colour coded as light blue top. Though this is the preferred method however a few assays have now allowed use of heparinised or EDTA plasma. So checking with your lab before sampling would be a good idea. Sample should be delivered to the lab immediately preferably in less than an hour at 15-22^{0}C in vertical position.[3]

Measures:

Multiple assays have been developed; the main principle is capturing the D-dimer fragment with a monoclonal antibody and detecting it quantitatively or qualitatively. Commercially different companies use different D-dimer epitopes, differ in their detection methods and also differ in their standards and instruments. Some of the more common methods include quantitative methods like enzyme linked immunosorbent assay (ELISA), enzyme linked immunofluoresence assay (ELFA), latex enhanced immunoturbidimetric method and qualitative method like the whole blood point of care tests (Table1).[4]

The D-dimers measured may be reported as fibrinogen equivalent units(FEU) or D-dimer units (DDUs) of mass per volume. One FEU is approximately twice one DDU mass. Different labs use different units such as mg/ml, µg/ml, µg/l, ng/ml etc... So it must be remembered that

1µg/ml = 1000 ng/ml= 1mg/L

Table 1: Different tests for D -dimer Assays

S.No.	Technique	Principle	Sensitivity	Description	Remarks
1.	ELISA/ELFA	Plasma added to wells coated with anti-d-dimer antibodies	High	Quantitative	Time consuming Labour intensive
2.	Latex-bead Assays	Latex particles coated with anti D-dimer antibodies	High	Qualitative Semi-quantitative	Usually manual
3.	Latex-based automated assays with immunoturbidimetric readings	Immunoturbidimetric readings taken on automated coagulometers	High	Quantitative	Rapid Automated
4.	Whole blood Assay Point of Care	Hybrid bi specific antibody used one for D-dimer and another for red cells membrane antigen	Low Observer dependent	Qualitative	RBCs agglutinate if d-dimer present.

As all labs differ in their methodology and reporting units, it is impertinent for the clinician to understand and interpret accordingly. The international community is trying to address the issue of lack of standardisation and need for harmonisation.[5,6]

Utility:

Over the years the main use was in identifying the thromboembolic events such as deep vein thrombosis (DVT), pulmonary thromboembolism (PE) and disseminated intravascular coagulation (DIC). It was part of various scoring systems like Well's score and Geneva score that divided the patient into groups of a low, moderate or high probability of having DVT/PE.[7,8] The lower cutoff values of D-dimer were used to increase the sensitivity of the test, however this limited the specificity of the test, so various strategies were used to increase the clinical utility of the test. One such strategy was to do age adjusted D-dimer.[9] Low D-dimer levels may be seen in healthy individuals and these levels increase with increasing age. In a population based cohort there was a 2.5 times difference seen in patients over 70 years when compared to those less than 50 years.[9] However, some investigators don't agree with this age adjusted D-dimer strategy.[10]

Early studies in the emergence of pandemic Covid-19 reported coagulopathy and elevated D-dimer levels in 3.75-68% patients.[11,12] In addition D-dimer >1μg/ml was identified as one of the risk factors for mortality in adult patients with Covid-19.[12] Some other studies have found >2.14mg/L cut-off levels to predict disease severity and mortality.[13] Lippi etal found that D-dimer values were enhanced in 36-43% positive patients with covid-19.[14] Recently a pooled analysis was done, the authors searched all the articles in Medline, Scopus and web of Science using the keywords laboratory and COVID-19 or Coronavirus 2019. They found 80 articles, majority were excluded and they analysed five studies which reported the difference in

D-dimer values in Covid-19 patients with and without severe disease. The results of the pooled analysis showed that D-dimer values were higher in the patients with severe disease as compared to those with milder disease. They concluded that increasing D-dimer levels may be associated with evolving worse clinical disease. [15] Another study by Tang et al concluded that disseminated intravascular coagulation criteria were fulfilled more frequently by the patients who died in hospital as compared to those who recovered (71.6 vs. 0.6%).[16]

The available data suggest D-dimer as a prognostic and mortality marker in severe Covid-19 patients. However, its value in a mild disease is an ongoing area of research. A recent meta-analysis of 18 studies showed that patients with positive D-dimer levels have two-fold higher risk of developing severe disease and four-fold higher risk of mortality.[17] Apart from the baseline value, certain trends (increasing values) have also been linked with significantly greater risk of venous thrombo-embolism, mechanical ventilation and all-cause mortality.[18]Likewise, Covid-19 management guidelines issued by Ministry of Health and Family Welfare (MoHFW), Govt of India recommend d-dimer testing in all moderate and severe Covid-19 patients at baseline and at serial intervals.[19]

To conclude, D-dimer is an important prognostic marker in Covid-19 that can give vital information on the thrombotic state of patients with moderate to severe disease. From a clinical perspective, it is often used to guide anticoagulant treatment decisions in these patients. Besides available evidence, proper patient selection, timing of test and frequency of serial evaluation are certain important research questions that need to be addressed in future studies.

If one understands the D-dimer test keeping its assay and units in mind then, it will help identify the worsening clinical picture of the Covid-19 positive patient. Otherwise the test may mislead the clinician into a false sense of improving/ deteriorating clinical condition of the Covid-19 patient. Therefore one must diligently glean information from this valuable test.

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Platelet rich plasma- a versatile therapeutic invention

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ABSTRACT

Platelet- rich plasma (PRP) is a recent invention in the field of medicine. Its predominant effects are due to the growth factors present in it which have major biological role in the body. These growth factors promote regeneration and tissue healing. Consequently, PRP has found use in diverse specialties like cardiology, dermatology, orthopedics, dentistry, gynecology and maxillofacial surgery. As it is autologous, there are minimal side effects and has no risk of transmission of diseases. This review focuses on the biology and diverse indications of PRP in medical sciences and also discusses few areas of caution while using this immensely versatile blood product.

INTRODUCTION

Platelet-rich plasma (PRP) is an autologous blood product which is rich in innumerable growth factors required for homeostatic processes of the body. The active ingredient includes platelet alpha granules which contain more than 30 growth factors like platelet derived growth factor (PDGF), transforming growth factor- alpha (TGF-b), epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), etc.[1] These growth factors stimulate cells like osteoblasts, adult mesenchymal stem cells, endothelial cells, fibroblasts and epidermal cells, thus promoting tissue healing, angiogenesis, collagen synthesis, matrix formation and osteoid production.[2]

HISTORY

The roots of PRP were sown when Matras et al described the use of a fibrin glue as a sealing substance so as to aid in healing tissues in various oral and maxillofacial surgeries.[3] Ferrari et al used it in 1987 as an autologous transfusion product to aid the patients in cardiac surgeries.[4] In early 1990s, multiple reports and studies in maxillofacial and periodontal surgery came up which showed dramatically improved healing properties of PRP. In the early 2000's, the use of PRP expanded into orthopaedics and sports medicine.[5] Currently, its use has expanded in almost all the medical specialties.

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Types of PRP

PRP contains more than 90 percent platelets, where as normal blood contains only 6 percent platelets. Ehrenfest et al have defined four main families of PRP:[6]

1. Pure PRP or leucocyte-poor PRP are preparations without leucocytes and with a low-density fibrin framework after activation.
2. Leucocyte PRP are preparations with leucocytes and with a low density fibrin

network after activation. It is the most commonly used product.

3. Pure PRP are preparations without leucocytes and with a high-density fibrin network. Such preparations exist in a strongly activated gel and cannot be injected.

4. Leucocytes and platelet rich fibrin (L- PRF) are preparations with leucocytes and with a high density fibrin network.

Methods to prepare PRP

A number of protocols are available for the production of PRP.[7] All these involve a centrifugation process which may be manual or automated. The volume of the blood sample taken, the anticoagulants used, the number of centrifugations and the respective time and centrifugal force differ in different protocols. The most commonly used method has been described below.

Ten millilitre of venous blood is withdrawn by means of a wide bore needle and a vacutainer containing an anticoagulant. Commonly used anticoagulants include heparin, citrate, acid citrate dextrose (ACD) and citrate-theophylline-adenosine- dipyridamole (CTAD). Double centrifugation is done. First centrifugation being slow to avoid gyrating down platelets and to isolate plasma, is done for ten minutes at 1600 rpm. After the first centrifugation, three layers are seen- red blood cells, buffy coat layer containing platelets and leucocytes and the topmost layer of plasma. Platelets are concentrated on top of the buffy coat layer. The supernatant plasma along with the buffy coat is withdrawn and re-centrifuged. Second centrifugation is done for ten minutes at 4000 rpm, after which the platelets separate and form a grayish pellet at the bottom of the tube and the rest being platelet poor plasma. About 1 ml of this platelet poor plasma is decanted off and the platelet pellet is resuspended in the remaining plasma to get PRP. With 10 ml blood, about 1-1.5 ml of PRP is obtained.[7]

The optimum concentration of platelets in PRP has been found to be 2.5 times the baseline. Above this concentration, there are no added advantages, rather it may be derogatory.[8] PRP activation prior to injection is another parameter that requires further discussion. Activation of platelets in PRP results in rapid growth factor release, with 90% of the prefabricated factors released in ten minutes. Many growth factors have short half-lives, so greatest efficacy may result if they are activated at or just prior to injection. PRP can be activated exogenously by mechanical trauma, thrombin or calcium chloride. Once PRP is activated, a fibrin network begins to form, solidifying the plasma and creating a fibrin clot or membrane. If PRP is activated too strongly, the fibrin network will be an unstable, bivalent network. A tetramolecular stable network forms if it is activated in a more physiologic manner.[9] Although this can be useful for surgical procedures, it is undesirable to have the PRP overly viscous when injecting into soft tissue or skin. Thus, most protocols use large bore needles (>22) to draw the blood and re-inject PRP to avoid unintentional activation of platelets.[10]

Some centrifuges offer specific braking mechanisms to prevent unintentional activation. The optimal regimen to prevent unintentional activation is not clear. PRP, when used in soft tissue does not need to be exogenously activated as collagen is a natural activator of PRP. Heat also activates PRP so the preparation room temperature should be around 20-22 degree so as to avoid

unintentional activation of PRP, temperature controlled centrifuges can be used for better efficacy.[10]

Indications in various fields of medicine

1. Cardiology

   It was used as an autologous blood product for transfusion.[4] It is being used to prevent deep sternal wound infection in patients undergoing median sternotomy for cardiac surgeries.[11]

2. Dentistry and maxillofacial surgeries

   As PRP helps in the process of tissue and bone repair and healing, it is used to promote faster recovery of the alveolar socket after tooth extraction which is a very common dental procedure.[12] Multitude of growth factors enable it to be used as a regenerative product in periodontal surgery.

3. Otolaryngology

   PRP has been known to improve tympanic membrane healing in tympanoplasties. It enhances facial nerve regeneration. It has been used along with fat transplantation for atrophic rhinitis. It is beneficial for vocal cord scar healing as it enhances EGF, FGF and FGR1.[13-14]

4. Dermatology

   It has been used in androgenetic alopecia as it upregulates growth factors like Insulin like growth factor-1, fibroblast growth factor-7 and VEGF in dermal papilla and thus lengthens the anagen phase. It promoted the development of follicles and downregulates apoptosis.[15] As PRP has a role in extracellular matrix synthesis, thus it has a use in chronic non-healing ulcers.[16] The growth factors induce collagen synthesis, hence its role in acne scars, facial rejuvenation and striae distensae. Its use in melasma is mainly due to TGF-b1 which has been shown to decrease melanogenesis.[17] Recently, its use has spread to refractory nail disorders like nail lichen striatus and idiopathic trachyonychia where injections are given intramatricially.[18]

5. Orthopedics and sports medicine

   PRP is used in tendinopathies as it improves tenocyte proliferation, collagen deposition and endogenous growth factors.[19] As it improves pain, healing and graft quality, it is being used in ligament reconstructions and muscle strains.[20] As it promotes osteoid formation, it is increasingly being used in osteoarthritis which is a chronic degenerative condition refractory to treatment. In addition to this, PRP has also been used in spinal and joint fusion surgeries.[21-22]

6. Gynecology[23]

   Due to its regenerative and anti-infective role it has been used in lichen sclerosis, leukoplakia, cervical erosion, chronic endometritis, chronic endocervicitis, etc. It has a major role in infertility. It reduces inflammation, enhances the activity of progesterone receptors that stimulate the growth of endometrium and improves egg quantity and quality. It nurtures ovarian rejuvenation which makes it useful for ovarian failure.

7. Plastic surgery

   PRP is being used to improve function of fat grafts during tissue engineering application as it stimulates adipose tissue-derived stem cells. It has also been used in chronic ulcers, breast reconstruction, etc.[10]

8. Neurosciences

   Due to its regenerative and anti-inflammatory properties, it has been used in ankylosing spondylitis, spinal injuries, disc protrusion, kyphoscoliosis and carpal tunnel syndrome among other indications.[19]

Adverse effects

Being autologous, the adverse effects of PRP therapy are rare and minimal which include pain in the injected area, infection, skin discoloration, allergic reaction and blood clot formation.[8] There have been very few case reports of severe allergic reaction to PRP.[24] It is hypothesized that it may be due to calcium chloride or thrombin used to activate it before use. There has been one case report of permanent blindness in a patient which occurred after periocular PRP which was done for glabellar rhytids by an unlicensed professional.[25] It was hypothesized that it may have occurred due to inadvertent intravascular injection of PRP filler. Some patients may develop transient regional lymphadenopathy due to exaggerated immune response induced by leukocytes and monocytes present in PRP.[26] Rare side effects like serum sickness like reaction have also been documented.[27]

Contraindications

a. Absolute contraindications[21]

· Platelet dysfunction syndrome and Critical thrombocytopenia- Anticoagulants used to prepare PRP like citrate, theophylline, adenosine and CTAD are specific inhibitors of platelet function. Theophylline and dipyridamole inhibit cAMP phosphodiesterase activity and adenosine stimulates membrane adenylyl cyclase, which consequently leads to an increase in platelet cAMP and inhibition of calcium mediated responses leading to a reduction in platelet activation. Thus, PRP is contra-indicated in patients who already have low or dysfunctional platelets.[24]

· Hemodynamic instability- In such patients, it is impossible to assess the blood profile and thus the response to PRP may be very severe and aberrant.

· Septicaemia- As PRP enhances chemotaxis, thus in patients with septic shock who are already in a condition of cytokine storm, it may lead to sudden deterioration.

· Local infection at the site of the procedure

· Patient unwilling to accept risks

b. Relative Contraindications [24]

· Consistent use of NSAIDs within 48 hours of procedure- Use of NSAIDS increases the bleeding tendency of the patient and it also causes thrombocytopenia.

· Corticosteroid injection at treatment site within 1 month

· Systemic use of corticosteroids within 2 weeks- It causes a pro-coagulant state which may result in an aberrant response to PRP.

· Tobacco use – Also causes a pro-coagulant state.

- Recent fever or illness – As PRP may induce a serum sickness like reaction or may induce fever in some patients, thus it should be used with caution in such patients.
- Cancer- especially hematopoetic or of bone- There is a controversial risk of growth factors in PRP inducing cellular proliferation and thus increasing cancer risk. But this seems more of a theoretical risk as these growth factors do not induce proliferation of cells with abnormal gene expression. The mitogenic effects of PRP are only limited to augmentation of the normal healing process and is theoretically not mutagenic, as the growth factors released do not enter the cell or its nucleus, but only bind to the membrane receptors and induce signal[1] transduction mechanisms.
- HGB < 10 g/dl
- Platelet count < 10^5/ul

CONCLUSION

PRP promotes inherent hemostasis and repair. It contains growth factors which are native and in their biologically determined ratios. As it is autologous, it is free from blood transmissible diseases like HIV and hepatitis. PRP is an autologous blood product which due to its extensive regenerative, anti-inflammatory and anti-bacterial properties has been successfully used in a number of fields of medicine.

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Secondary mandibular reconstruction using a free fibula microvascular flap in surgical management of ameloblastoma

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ABSTRACT

Mandibular ameloblastoma is a well known neoplasm whose surgical treatment has been controversial till date. Conservative approach has a significant risk of recurrence while radical approach is often associated with functional and aesthetic deformity. Reconstruction of mandibular defects to restore proper form and function of mandible especially in young patients poses a great challenge. A staged approach for management of ameloblastoma was used in the present patient. A combined approach of an immediate reconstruction with reconstruction plate allowing better monitoring for a disease-free period followed by secondary reconstruction with free fibula flap led to successful rehabilitation of functionality and aesthetics in the present patient .

Keywords: Mandibular ameloblastoma , fibula free flap, secondary reconstruction.

INTRODUCTION

Segmental resection of mandible is a common ablative procedure in the surgical management of jaw tumors (benign and malignant), cysts, osteoradionecrosis, etc. Reconstruction of large jaw bone defects presents a major challenge as proper bone reconstruction is important to provide comprehensive and aesthetic oral rehabilitation. Small jaw bone defects can be easily reconstructed using non-vascularised bone grafts, but the outcome remains unpredictable . As the bone graft size increases, chances of graft resorption and its failure increases.[1] Hence, reconstruction of large bone defects with vascularised bone flaps using microvascular reconstructive technique is the only viable option. We present a case of young female patient who has been successfully treated by segmental resection for jaw tumor with a primary reconstruction an implant and a secondary reconstruction with fibula free flap in the interval period.

CASE REPORT

A 19-year old female presented with swelling of left lower jaw (Fig. 1a,b). Routine blood investigations, x-rays and incisional biopsy were done to confirm the diagnosis. Histopathology was suggestive of ameloblastoma. CT revealed gross expansion with full thickness involvement in the body region of mandible. She was planned for segmental resection of tumor with 1cm bone margins to prevent recurrence. A segmental resection of the mandible under general anesthesia was done and bone defect was reconstructed primarily using titanium reconstruction plate to

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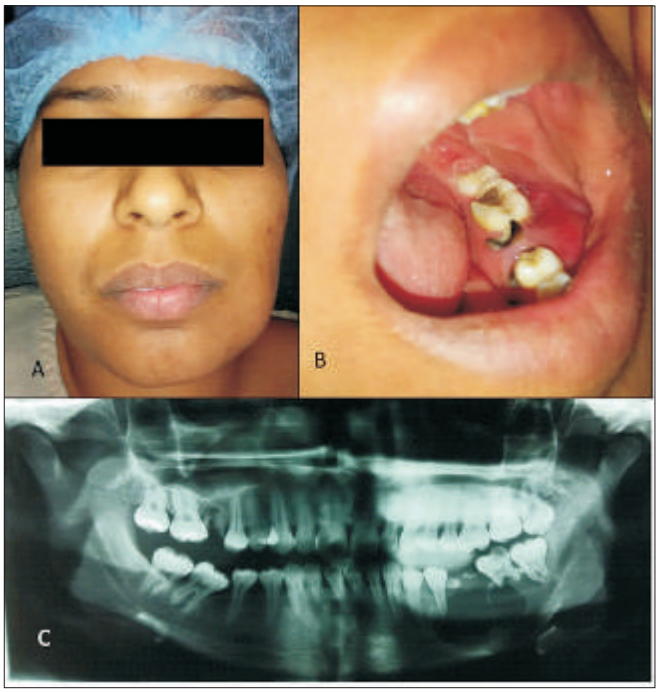

Figure 1: (A)- Preoperative facial photograph showing swelling over left mandibular body region. (B)- Preoperative intraoral photograph showing expansion of mandibular bone both buccally and lingually. Displacement of teeth can also be noticed. (C) - Preoperative orthopantomogram showing multilocular cytic radiolucency at left mandibular body region with cortical expansion and displacement of associated teeth.

prevent collapse of dental occlusion. The healing was uneventful and patient recovered quickly.

After 2 years, she came for second stage reconstruction for aesthetic and cosmetic improvement. Orthopantomogram was done to evaluate the status and no recurrence was detected. The bone defect was measured to be 6.5cm and fibula free flap was planned. X-ray and Doppler scan of both legs were done to rule out peroneal magnus artery and assess the quality of leg vessels and bone. Fibula bone flap was harvested along with peroneal vessels from ipsilateral leg under tourniquet control and general anesthesia (Fig. 2a,b). Simultaneously mandibular bone defect was exposed through previous skin scar and facial vessels were prepared. All preparations at the recipient site were done before disconnecting the flap from leg to minimize ischemic time. Immediately, the bone flap was transposed into the face and trimmed to fit snuggly into the jaw bone defect site and fixed with pre-existing reconstruction plate using titanium screws. Anastomosis of peroneal artery with facial artery and peroneal vein with common facial vein were done using 10-0 Nylon suture under surgical microscope. After anastomosis, the vascularity of flap was checked and there was good flow and no leakage in anastomosed vessels (Fig 2c). Both recipient and donor sites were closed layer wise and suction drain was placed. She had uneventful recovery and was advised to walk on 5th postoperative day with support. She was discharged on 8-day and advised to avoid lifting any heavy object till 1-2 months. At 1 year follow up, x-ray showed good bone union and no bone

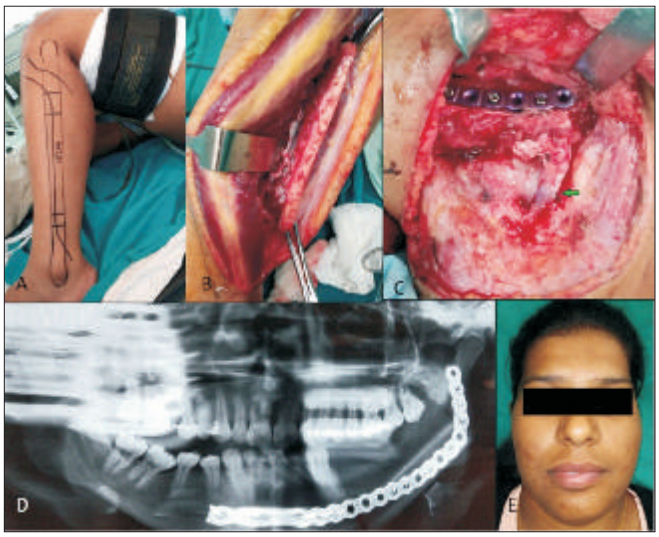

Fig 2: (A)-Intraoperative photograph of leg showing markings of fibular flap. Torniquet which was used during the harvesting of flap is also visible. (B)-Intraoperative photograph showing osteotomized fibula bone with peroneal vessels on the deeper side. (C)-Intraoperative photograph showing transplanted fibula bone in the mandibular defect fixed with titanium reconstruction plate. Green arrow shows the anastomosis site of peroneal vein (donor) with facial vein (recipient). (D) - Postoperative orthopantomogram showing stable transplanted fibula bone reconstructing the bone defect. (E) - Postoperative facial photograph showing facial symmetry and good esthetics.

resorption (Fig. 2d). Patient was highly satisfied with the aesthetic and functional outcome . No morbidity at both recipient and donor site was observed (Fig.2e). Patient further underwent dental rehabilitation with dental implants as an interval procedure .

DISCUSSION

Mandibular ameloblastoma is commonly occurring locally infiltrative, benign odontogenic tumor, accounting for 80% of all ameloblastomas .[2] Approximately 10-15 % of all reported cases of ameloblastoma are in younger age group (< 19 years) and more than two thirds of them are younger than 40 years .[3] The clinical symptoms may range from slow growing bony swelling, pain, displacement of teeth, paresthesia or insignificant findings in initial stage of tumor. This often leads to late diagnosis of tumor, often attaining enormous size which poses a challenge to treatment both in terms of planning, reconstruction and its tendency for recurrences.

Two strategies have been advocated for management: (a) conservative surgery which includes enucleation, curettage, marsupialization (b) radical approach i.e. resection of tumor with safe margins , with or without continuity defect of mandible. However, conservative approaches such as curettage have 55-90% rate of recurrence as these methods leave microscopic island of tumor cell in bone.[4] But a definitive radical approach as primary treatment modality has low recurrence rate. Radical approaches often lead to severe cosmetic and functional problems if not addressed properly in terms of reconstruction.

Mandible forms major part of one's appearance and has important role in functioning of masticatory complex. Resection of mandible can lead to abnormality in jaw functioning, speech, swallowing, oral competence and facial expressions. In younger patients, radical approaches such as segmental resection can affect patients psychologically in terms of facial appearance and give a major setback to their physical image and self-confidence. Therefore, reconstruction of such jaw defects is indispensable specially in today's era where multiple reconstructive options are available .

Segmental mandibular defects can be approached variably for reconstruction depending on extent of tumor, patient's age, other comorbidity, disease prognosis and expertise of the surgeon. Jaw defects after ablative surgery can either be reconstructed immediately (primary) or delayed (secondary) with its own advantages and disadvantages. Delayed reconstruction allows recurrence monitoring and clearly establishes tumor-free margins histologically. Staged reconstruction allows good oral seal which ensures no contamination with saliva and oral bacteria thus increasing success of graft. Lawson et al reported 90 % success rate with delayed reconstruction, compared to 46 % with immediate reconstruction when using non-vascularized bone grafts.[5]

Jaw reconstruction has evolved from use of reconstruction plates with or without bone grafts, non-vascularized bone grafts, variety of free vascularized bone flaps, distraction osteogenesis, modular endoprosthesis and tissue engineering . The use of reconstruction plates in initial surgery is beneficial in terms of less operating time, no donor site morbidity and minimal technical expertise as compared to microvascular surgery. Few of the complications of reconstruction plates include plate fracture, screw loosening, fistula formation, plate exposure, wound dehiscence, cutaneous necrosis and inadequate aesthetics if plate is improperly contoured. Arden et al reported that

extirpative losses of more than 5 cm of bone are associated with unacceptably high complication rates of 81% when plates alone are used to repair lateral defects.[6]Due to limited life span of reconstruction plates, secondary surgery is often required to restore continuity defect. Dental rehabilitation is another important consideration specially in young patients who surpass disease free period. Pogrel et al found vascularized flaps has better outcome when defect size is greater than 6cm.[7] Therefore, vascularized bone free flap is first choice when bone defects larger than 6cm are planned to reconstruct. They have reliable success rates as the bone doesn't undergo creeping substitution which leads to rapid healing, revascularization and osseointegration. Dental rehabilitation with implants can be done as one single staged procedure and planned in short span of time.

Fibula has rich blood supply from endosteal and periosteal artery which allows multiple osteotomies to give proper arch form without causing any bone devascularisation.[8] Fibula amongst all flaps provide maximum bone length upto 25cm which can be used to reconstruct whole of mandible.[9] Fibula harvesting allows two-team approach simultaneously. The minimal donor site morbidity is one of the advantages of fibula flap. The stability of ankle joint is unaffected if 7cm of bone is preserved at distal end.[10] Some patients may experience post operative pain on ambulation, however, the present patient had no such morbidity. Fibular flap is based on peroneal artery, a branch of tibioperoneal trunk traverses along the medial aspect. Peroneal vessels provide adequate pedicle length (2-4cm), which can further be increased by harvesting distal portion of bone and subperiosteal soft tissue dissection in proximal portion. Fibula flap is excellent reconstructive option for mandibular reconstruction involving large defects. It provides proper facial aesthetics and functional form with reliable success rates and patient satisfaction.

Ethical considerations: No ethical issues involved

Funding sources: None declared

Disclosures: No conflict of interest declared

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Bullous adverse reaction to extravasation of large volume blood and blood component transfusion

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ABSTRACT

Blood transfusions through blocked peripheral venous cannula can lead to variety of local and systemic adverse effects. An unusual localised adverse reaction of bullae formation with necrosis on dorsum of left hand clinically mimicking necrotising soft tissue infection following packed red cell transfusion is being reported. Importance of extravasation injuries and monitoring the patency of intravenous catheters throughout transfusion is being highlighted.

Keywords: Bullae, blood transfusion, intravenous catheters, transfusion reaction , extravasation

INTRODUCTION

Blood transfusion is a common supportive intervention in both medical and surgical treatment in wide variety of medical conditions. Local adverse effects of transfusions depend upon infusate and its uninterrupted flow through the veins. Large volume rapid intravenous infusion through blocked cannula can lead to extravasation of fluids leading to edema and bulla formation . We hereby report an unusual case which was referred to us as an allergic transfusion reaction but ultimately turned out to be a bullous injury resulting from extravasation of blood product through a blocked peripheral venous cannula.

Case Report

A 25-year- old woman developed a left uterine horn rupture with 1 litre of hemoperitoneum and 500-600 gram of clots recovered during emergency surgery. She was rapidly transfused around 2.5 litres of normal saline, five units of fresh frozen plasma (1 litre) and 2 units of packed red cells (550 ml) through a peripheral 18G cannula as she underwent surgical intervention. Patient had a thin built and the peripheral venous cannula was placed on lateral aspect of wrist joint extending on to dorsum of left hand. When the patient was being transfused the third packed red cell unit in operation theatre, appearance of bullae were noticed on dorsum of left hand. On examination, two fluid filled hemorrhagic bullae with necrosis were seen with larger one measuring 5x3 cm (Figure 1). Other laboratory work up related to haemolytic transfusion reaction was normal . Blood bag, patient blood and bullae fluid culture were all sterile on bacteriological culture, excluding infection. The intravenous tranfusing cannula was found to be blocked and thus necrosis and bullae formation was ascribed to be due to extravasation of fluids. Bullae were aspirated aseptically and a pressure dressing and patient was prescribed 2 % mupirocin cream twice a day for one week. Patient was asymptomatic after one week.

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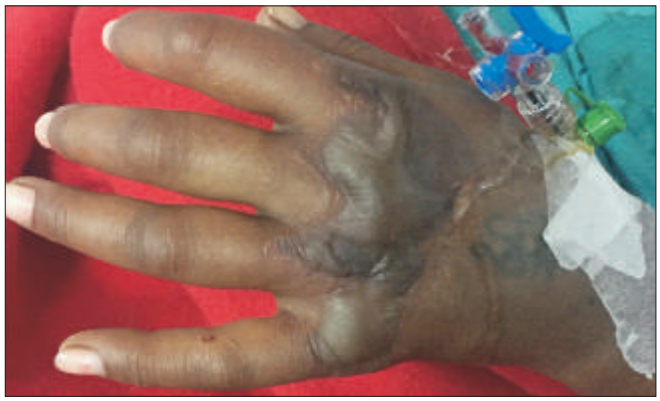

Fig. 1: Dorsum of hand showing hemorrhagic bullae at the site of cannulation.

DISCUSSION

Blood transfusions should be monitored throughout the process as adverse reactions may develop at any point of time during the course of transfusion. Ensuring the patency of peripheral venous cannula at all time during transfusion is very important along with monitoring vitals of the patient as fluid administration through the blocked cannula can lead to fluid leak or extravasation into surrounding tissue spaces which can cause damage to the surrounding tissues by mounting an inflammatory reaction . The extent of tissue damage following such extravasation depends upon the type, volume, pH and osmolarity of infusate and may range from minor tissue injury to significant tissue necrosis with long term sequelae. Sometimes the sequelae can be more disabling than the primary illness and add significantly to morbidity of the patient 1. Literature reports skin or vessel fragility, low muscle to subcutaneous tissue mass and inability to report pain as the various risk factors associated with extravasation. Dorsum of the hand and foot, ankle, antecubital fossa are usually implicated in extravasation injuries due to little soft tissue protection for underlying structures in these anatomical locations. Joints and creases are also susceptible to such extravasation due to small anatomical space .2,3 In present case, patient was a thin built female and cannula was placed on dorsum of hand predisposing it to extravasation.

Extravasation injuries have often been reported with chemotherapeutic agents, but are uncommon following transfusion of blood components. Nonetheless, blood products due to their varying pH can lead to tissue damage following leakage. Sakakibara et al reported bullae after rapid blood transfusion following blockade of peripheral venous access. 4 Though no pressure system was applied in the present case, but large volumes of fluids including blood components were rapidly administered in a thin built female through the blocked peripheral venous cannula which was placed on dorsum of hand. This might have led to bullae formation in the present case. Awareness regarding such extravasation complications among treating physicians /clinicians and their paramedical supportive staff is very important to ensurer early recognition, proper management and avoiding confusion with potentially serious allergic transfusion reactions.

Ethical considerations: No ethical issues involved

Funding sources: None declared

Disclosures: No conflict of interest declared

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Gastrointestinal stromal tumor simulating an ovarian tumor

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ABSTRACT

Gastrointestinal stromal tumor (GIST) is the mesenchymal neoplasm of gastrointestinal tract, arising from interstitial cells of Cajal, most commonly located in the stomach and proximal small intestine. The clinical and imaging features may mimic an ovarian tumour due to its non-specific symptoms and / or imaging characters. A rare case of GIST presenting as an ovarian tumor, clinically and radiologically in terms of location in a postmenopausal woman is being presented. Imaging revealed midline heterogeneous large lobulated mass in pelvis, surrounded by very prominent tortuous vascular channels draining into superior mesenteric vein and splenic vein. Fine needle aspiration cytology led to the unexpected diagnosis of GIST while laparotomy revealed a large peritoneal pelvic mass arising from the ileum with normal uterus and adnexa.

Keywords: Gastrointestinal Stromal Tumor, Ovarian tumor, Fine needle aspiration cytology

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are rare mesenchymal neoplasms of gastrointestinal tract with an estimated incidence of approximately 1/100000 per year.[1] Many of these tumors are detected incidentally as bystanders during imaging or surgical intervention being done for other indications as these are largely asymptomatic. Because of their location these tumours may often be confused with a pelvic mass specifically ovarian tumor. In absence of specific clinical features, preoperative diagnosis may not be always possible. The mainstay of confirmation of diagnosis is histopathology and immuno-histochemistry.[2] In the present case due to pelvic location of the mass, it was mistaken to be an ovarian tumour and provisionally diagnosed to be malignant epithelioid stromal tumor. Intraoperatively findings showed origin of the tumour mass which was subsequently confirmed to be GIST on histopathology and immuno-histochemistry.

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CASE REPORT

A 75-year-old multiparous postmenopausal female presented with shortness of breath of two to three months duration. There was history of loss of appetite and weight for two months without any bowel and bladder complaints. On chest examination, the breath sounds were decreased on right side. Per abdomen examination revealed an ill-defined, immobile, non-tender, firm mass of approximately 10 × 10 cm with variegated feel, extending into the pelvis. On bimanual examination uterus was not felt separately from above mass. Per speculum examination showed the cervix flushed with vagina. Clinically, a possibility of ovarian mass was, thus considered.

Ultrasound abdomen showed bilateral pelvic adnexal mass, right sided 9.4 x 9.2 cm, solid large well-defined mass, left sided lobulated heterogeneous mass measuring 6.5 × 2.6 cm. and gross right sided pleural effusion. Contrast enhanced computed tomography (CECT) abdomen revealed a right sided heterogeneous 10x7x10 cm lobulated mass in pelvis and right ovary could not be visualized separately due to surrounding prominent tortuous vascular channels draining into superior mesenteric vein and splenic vein. Midgut volvulus of congenital variety needing no intervention was also noted. Left ovary was visualised and found normal. CECT chest revealed a moderate right sided hydropneumothorax, with underlying lung atelectasis, a right ovarian mass lesion with midgut volvulus with small bowel obstruction and mild ascites. Contrast enhanced magnetic resonance imaging (CE-MRI) pelvis was suggestive of midline pelvic heterogeneous 9x10x11 cm mass, displacing adjacent bowel loops, soft tissue structures and vessels (Figure 1). Intervening fat planes were maintained. There was no lymphadenopathy or significant free fluid in the abdomen. Therapeutic pleural fluid tap drained 700 ml which was exudative, non-tubercular and negative for malignant cytology. Because the right ovary could not be visualized clearly and separately, a provisional diagnosis of malignant right ovarian mass was considered. Serum CA-125 was 173 U/ml, CA 19-9 and CEA levels were found to be within normal limits. Fine needle aspiration cytology (FNAC) showed spindle cell tumor suggestive of GIST. Immunohistochemistry staining for CD 117 confirmed the diagnosis of GIST.

The patient underwent an exploratory laparotomy that revealed a large peritoneal pelvic mass measuring 15 x 12 cm, arising from the ileum, which was adherent to the omentum , 150 cm distal

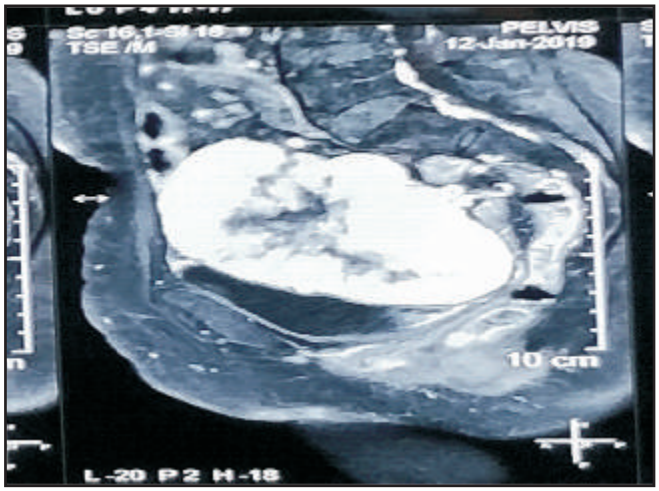

Fig. 1: Abdominopelvic mass as seen on Contrast enhanced MRI (CEMRI).

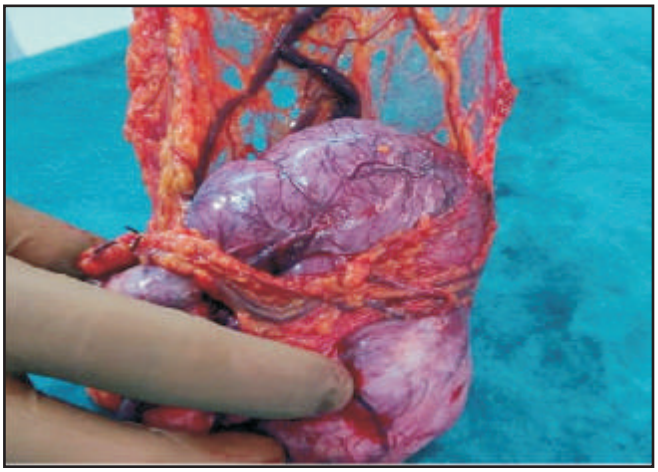

Fig. 2: Vessels of the abdominopelvic mass can be seen draining into superior mesenteric (red arrow) and splenic veins (yellow arrow).

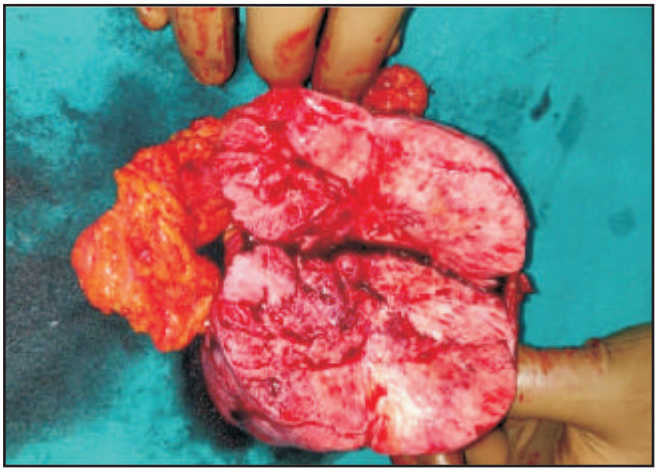

Fig. 3: Variegated appearance of tumor on cut section

to the duodenojejunal junction (Figure 2 & 3). Mass was resected with one cm of ileal margin on each side and end to end anastomosis was performed. Bilateral adnexa and uterus were normal. There was no lymphadeno-pathy. Resected tumour further confirmed the diagnosis of intestinal GIST on histopathology and immunochemistry.

DISCUSSION

Diagnosis of GIST should be substantiated with a rapid and accurate preoperative cytology as it is important to offer a timely targeted therapy to those with metastatic or unresectable tumour.[3] Gynaecologists need to be cognizant of atypical extra-ovarian pathologies which can present as pelvic mass mimicking gynaecological malignancies. GIST may simulate gynaecological masses like ovarian malignancies, tubo-ovarian mass and leiomyomas. Present case highlights the diagnostic potential of FNAC in the evaluation of pelvic mass, which was clinically and radiologically resembling a malignant ovarian pathology. Histopathological diagnosis is also very important for early and prompt neoadjuvant chemotherapy in ovarian cancer.

Present patient had several findings which suggested consideration of an alternative diagnosis or made the diagnosis of malignant ovarian pathology. The blood supply surrounding the tumour mass was more proximal and central, draining in to superior mesenteric and splenic veins rather than in iliac vessels. Moreover, the amount of pleural effusion was disproportionate to mild ascites. Some overlapping features can further help in clinching the correct diagnosis. Ascites is absent or mild in GIST while symptoms of intestinal obstruction may be seen early in the course of disease in GIST as compared to malignant ovarian pathology. CA-125 range is low (6-160 U/ml) while CEA and CA-19.9 are rarely increased in GIST. In large GIST central necrosis with hypo echoic centre may help suspect non-ovarian pathology on imaging.[4] Various Immunohisto-chemistry markers which are positive in GIST include C-KIT (CD-117), CD34 and DOG-1.

Prognosis is dependent on site, size and type and mitotic figures calculated using risk tables.[5] Management is by resection of tumor & chemotherapy with imatinib.

CONCLUSION

Appropriate preoperative diagnosis for preparation and surgical intervention can be suspected for Non-gynaecological tumor like GISTs mimicking ovarian tumor only with high clinical suspicion with unusual clinical sign**s.**

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Ethical approval: Not required

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Dermatofibrosarcoma protuberans: report of cases and brief review of literature

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ABSTRACT

Dermatofibroma protuberans (DFSP) is a slow growing soft tissue tumour of unknown aetiology with an annual incidence of 1 / million . It is more commonly seen in males and usually presents as asymptomatic , small (1-5 cm) grouped, firm nodules on the torso. It may recur locally after excision but does not metastasize. Linked with a somatic mutation, it has many variants. Moh's micrographic surgery is generally recommended as the treatment of choice. Two cases with skin lesions reported to be DFSP on histopathology have been described.

Keywords: Dermatofibrosarcoma, protuberans

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is an indolent soft tissue sarcoma affecting skin and fat. Usually seen as a small nodule on the torso, the tumour has a great tendency to recur locally after surgical excision without any propenisity for distant metastases.[1] Two cases of histologically proven DFSP are presented and their management is being discussed.

Case 1

A 31-year-old female presented with complaint of an epigastric growth over a previous scar site from where a undiagnosed soft tissue swelling had been removed 5 years back (Figure 1). Since last 1 year, the scar site started having a pinkish swelling at one end of the scar with painless and spontaneous satellite growths with no abdominal complaints. Slight induration was present. It was fixed to the skin but not to the underlying structures. Histopathology from a core biopsy revealed the growth to be dermatofibrosarcoma protuberans. Magnetic Resonance Imaging (MRI) showed the mass to be a subcutaneous lesion approximately 2.5cm distal to the umbilicus with no fat stranding. Wide local excision was done under general anaesthesia (Figure 2). Histopathology of excised tissue further confirmed the diagnosis of dermatofibrosarcoma protuberans.

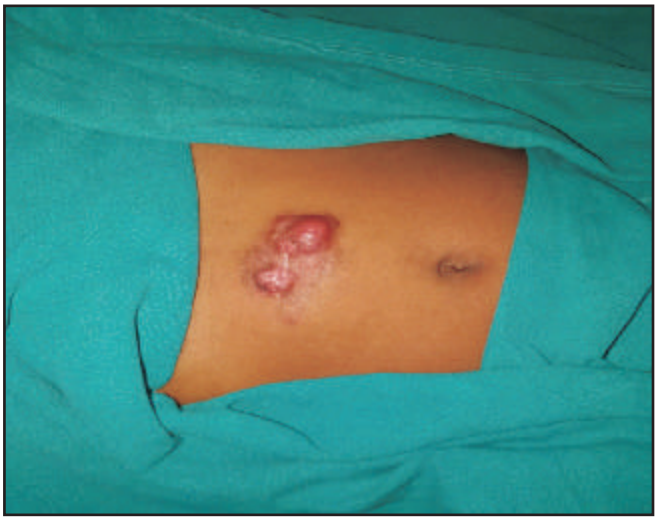

Fig. 1: Multiple nodular hard timorous lesions.

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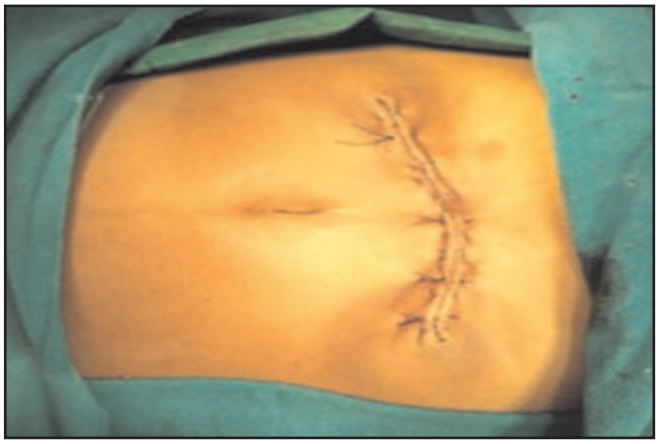

Fig. 2: Removal of lesions with wide local excision.

Case 2

A 50-year-old male presented with a cutaneous swelling over epigastric region of abdomen since 6 years. He had developed lipoma at the same site 11 years back which was excised uneventfully. The present lesion had an insidious onset, was gradually progressive, tender, skin coloured, not associated with any discharge, fever, loss of weight or appetite. On examination, there was a single 10x5 cm sized swelling in the epigastric region, which was well defined, globular, tender and hard in consistency. No surrounding induration or erythema were present. Ultrasound abdomen showed the lesion to be an abdominal wall soft tissue lesion suggestive of liposarcoma in view of the past history of lipoma over the same site. Fine needle aspiration cytology was suggestive of a spindle cell lesion suggestive of dermatofibroma. Contrast enhanced CT of the abdomen showed a heterogeneously enhancing lobulated mass in subcutaneous fat of epigastric region. A wide local excision of the mass was done under general anaesthesia and a multilobulated lump approximately 8x6 cm was excised. Postoperative period was uneventful and detailed histopathology examinated of the excised tissue confirmed it to be dermatofibrosarcoma protuberans.

DISCUSSION

Dermatofibrosarcoma protuberans, first Described by Taylor (1890), is a rare skin tumour with an indolent course.[2] The present term of DFSP was coined by Hoffman in 1925.[3] Its incidence is 1 per million people per year and the black population is more commonly affected.[1,4] It affects skin, fat and muscles, and causes tumours in the deep layers of skin. It occurs most commonly on the trunk (47%) followed by the arms (18%), legs (20%) and head and neck (14%) and is slightly more common in men (3:2) presenting in their thirties.[1,2] It begins as a small, firm patch of skin, 1-5 centimetres in diameter with 84% of the tumours measure less than 5 cm while 77% are generally superficial.[5] It typically grows slowly and can be seen as a plaque or nodule fixed to the dermis, a nodule being more common while surrounding skin may show telangiectasia. Fixation to underlying structures indicates an advanced disease. Also known as Darier-Ferrand tumour or Darier-Hoffmann tumour, 85 to 90% DFSP's are low grade lesions.

American Musculoskeletal Tumour Staging divides DFSP into:

IA: Low grade, Intracompartmental with only subcutaneous extension.

IB: Low grade, Extracompartmental. Involving muscle or fascia

Several variants of DSAP include : a Bednar tumour which is a pigmented DFSP as it contains melanin-containing dendritic cells, a myxoid tumour which contains myxoid stroma, a Giant cell fibroblastoma (juvenile DFSP) which affects children and adolescents and is characterized by prescence of giant cells, and a fibrosarcomatous DFSP which is more aggressive and more likely to metastasize.

Histologically, monomorphic, benign spindle cells are seen in a storiform pattern around central

vessels. A tumour free Grenz zone is seen in early disease.[2] DFSP is associated with a somatic (17; 22) translocation in nearly 90% of the cases. An abnormal combination of products of Collagen Type I Alpha1 (COL1A1) gene and Platelet Derived Growth Factor B (PDGFB) gene occur in excess which cause aberrant cell proliferation and differentiation[2]. COL1A1 gene makes Type 1 collagen. PDGFB gene makes an isoform(B) of the gene which stimulates proliferation and differentiation. Cells may stain positive for CD34 and Factor XIIIa.[2] A scar after a burn or surgery may increase the risk. Pregnancy may hasten growth of a pre-existing tumour.[4]

Treatment options include:

a) *Wide Local Excision (WLE):* Removing the lesion and a portion of normal-looking skin under local anaesthesia (LA) or GA. It is the commonest treatment with 90% local control. Bogucki et al reported higher recurrence after WLE but recent data shows lower overall recurrence rate (7.3%).[6]

b) *Moh's Micrographic Surgery (MMS):* removes one layer of skin at a time under LA with examination of each layer and continuing until cancer cells can no longer be found. It shows consistent margin control, high cure rates, lower recurrence and low morbidity.[7] Even with recurrent DFSP, Mohs surgery has a 98% cure rate.[4]

c) *Systemic Disease:* Adjuvant radiotherapy is considered if margins are positive[1]. Imatinib can induce regression in recurrent or metastatic disease.[8,9] Sjo¨blom et al showed efficacy of PDGF antagonist in DFSP.[2]

Preoperatively, MRI is beneficial for depth assessment and tissue involvement. Core needle biopsy may be used for histopathological diagnosis and FNAC can be employed in patients with recurrence.[9] The tumour has a tendency to recur. However, it does not often metastasize. Distant spread is rare and metastasis is hematogenous. Lymphatics may rarely be involved . If DFSP recurs, it is often within three years of treatment. The general prognosis is excellent but follow ups with the dermatologist may be recommended every three to six months for three years and annually thereafter.[4]

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Piperacillin-tazobactam induced pancytopenia in a polytrauma patient

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ABSTRACT

Critically injured trauma patients are often admitted to intensive care unit (ICU) for mechanical ventilation with supportive management. Adequate haemodynamic and haemostatic resuscitation is of utmost concern in these patients. We report a case of successful management of pancytopenia, in a young adult with polytrauma, after evaluating all differential diagnoses. A young male with alleged history of assault and multiple stab injuries, was admitted to ICU for monitoring and haemostatic resuscitation, after emergency surgery. Pancytopenia was seen on haematological examination on day 3, following which all possible causes of pancytopenia in a trauma patient were evaluated. A gradual improvement in the clinical condition as well as haematological parameters was seen by day 7 of ICU stay after discontinuing the antibiotic piperacillin-tazobactam. Apart from mechanical ventilation, the patient was meticulously managed with adequate antibiotic coverage and supporting therapies. The haematological recovery seen on discontinuing the offending drug, supports the diagnosis of drug induced reversible pancytopenia in the present case.

Keywords: pancytopenia; trauma; anaemia; antibiotic

INTRODUCTION

Critically injured trauma patients are admitted to intensive care unit (ICU) for mechanical ventilation and supportive management. Fever and pancytopenia is usually encountered in polytrauma patients on mechanical ventilation during the postoperative periods. Though, a high index of suspicion is required to clinch cases of neutropenia in infectious aetiology, it may not be seen in trauma patients. Drug induced pancytopenia usually develops on prolonged exposure to drugs, however, patients of polytrauma are often on multiple drugs at the same time and usually obtain higher doses of each drug due to life threatening situations. Adequate haemodynamic and haemostatic resuscitation is of utmost concern in these patients. We report a case of pancytopenia in a young adult with polytrauma developing pancytopenia due to possible exposure to piperacillin-tazobactam, Differential diagnoses of pancytopenia developing in the setting of polytrauma managed in intensive care unit is being discussed.

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CASE REPORT

A 26-year-old male with alleged history of assault and multiple stab injuries, was hospitalised. He was conscious and oriented with blood pressure of 102/60 mm of Hg, pulse rate of 118/ minute and

oxyhaemoglobin saturation (SpO_2) of 88% on room air. On auscultation, air entry was reduced on the right side of the chest. The arterial blood gas analysis showed hypoxemia with lactate value of 5.4 $mmol.L^{-1}$. An emergency surgery was performed for primary repair of inferior vena cava rent, anterior-posterior duodenal and caecum perforation with loop ileostomy. Intraoperatively, patient was transfused 2000 mL crystalloids, 500 mL colloids, three units of packed red blood cells and three units of fresh frozen plasma. An infusion of noradrenaline (0.35 $mcg.kg^{-1}min^{-1}$) was started due to hypotension. Postoperatively, ABG showed metabolic acidosis with lactate value of 7.0 $mmol.L^{-1}$. The patient was shifted to intensive care unit for further management, supportive care and mechanical ventilation.

On admission to ICU, the vitals were maintained. Patient received ceftriaxone 1 gm every 12 hourly intravenously, metronidazole 500 mg every 8 hourly infusion, supportive medicines and synchronised intermittent ventilation (SIMV). The initial postoperative blood investigations revealed haemoglobin (Hb): 8.4 $gm.dL^{-1}$, platelet count (PC) of 1.6 10^9. dL^{-1}, total leucocyte count (TLC) of 5700 $.mL^{-1}$, prothrombin index (PTI) of 72% and international normalised ratio (INR) of 1.37 (Table 1, Figure 1). Chest X-ray showed subcutaneous emphysema. Ultrasound (USG) abdomen revealed mild fluid in pelvis and mild pleural effusion. On day 2 of ICU stay, patient had intermittent fever episodes ranging from 99.4 F to 100.4 F (Table 1). Piperacillin-tazobactam (PTZ) 4.5 g every 6 hourly intravenously was empirically started and ceftriaxone was stopped. Ionotropic support was gradually tapered off. On day 3 of ICU stay, a decreasing trend in complete blood count (CBC) was observed. The Hb was 6.6 gm/dL, PC

Table 1
Investigations and temperature monitoring during intensive care unit stay

Investigations	Day 1	Day2	Day 3	Day 4 (Morning)	Day 4 (night)	Day 5	Day 6	Day 7
Hb ($gmdL^{-1}$)	8.4	7.1	6.6	3.9	6.7	7.1	8.4	9.2
PC ($\times 10^9$ dL^{-1})	1.16	1.08	0.75	0.46	0.74	0.77	0.81	0.89
TLC (mL^{-1})	5700	3900	1800	1800	3400	3600	3800	4200
Neutrophils (%)	76	77	15	16	78	80	76	75
Leucocytes (%)	17	15	3	5	15	12	15	20
Eosinophils (%)	4	6	1	2	5	4	5	3
Basophils (%)	0	0	0	0	0	0	0	0
Monocytes (%)	5	2	1	0	2	4	4	2
PTI (%)	72	88	64	84	88	100	100	100
INR	1.37	1.14	1.59	1.18	1.12	1.0	1.0	1.0
Temperature (°F)	100.7	99.4	102.4	100.6	100.2	101.2	99.3	98.8

Hb: haemoglobin, PC: platelet count, TLC: total leucocyte count, PTI: prothrombin index, INR: international normalised ratio

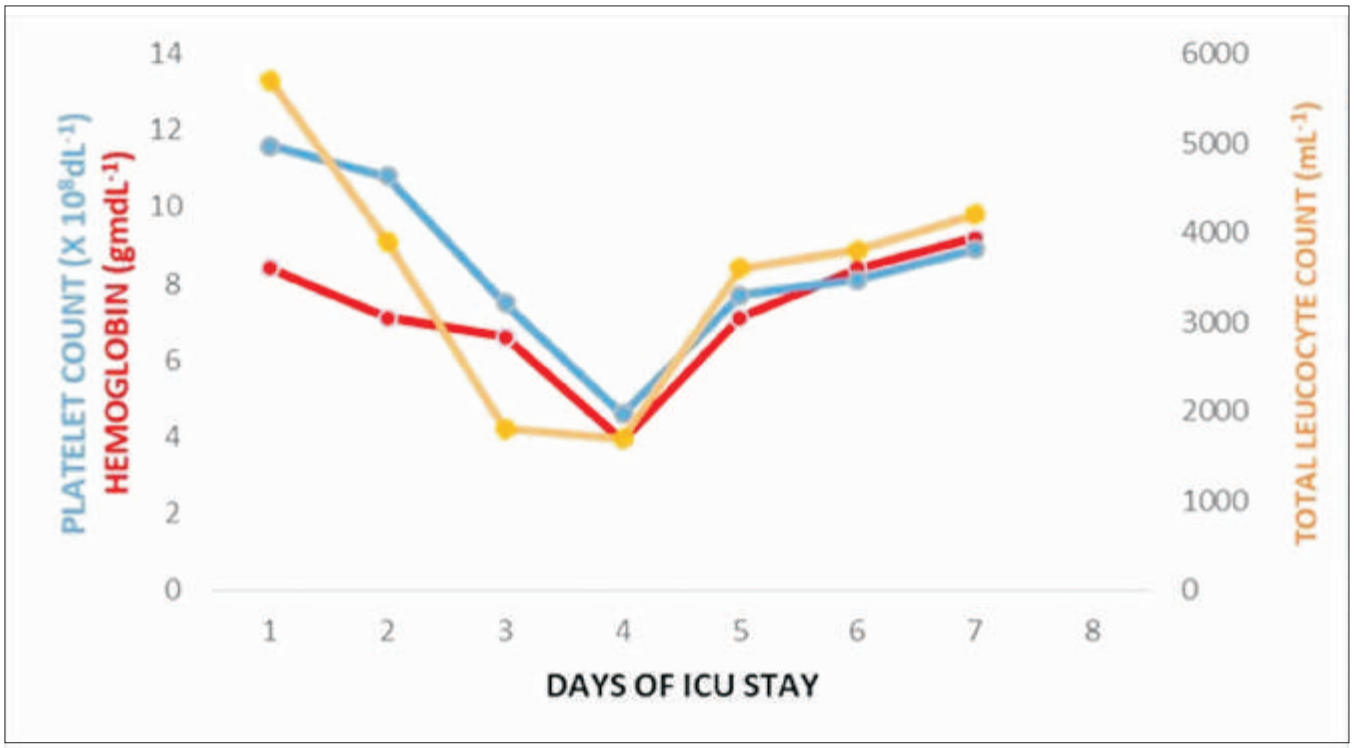

Figure 1: Line diagram showing changes in haematological parameters of the patient over a period of 7 days of ICU stay; Platelet count (108 dL-1); Haemoglobin (gm. dL-1); Total Leucocyte Count (mL-1)

was 0.75 10^9 .dL^{-1} and TLC was 1800 .mL^{-1} (Table 1, Figure 1). There was no evidence of active bleeding. Blood and urine culture reports were negative for bacterial infection. Peripheral blood smear showed reticulocytes and schistocytes with giant platelets. Repeat USG abdomen showed borderline splenomegaly. Subsequently, iron (iron sucrose 100 mg in 100 mL normal saline iv on alternate days), folic acid (5mg twice daily orally), vitamin B12 (1000 mcg iv on alternate days) were supplemented. Apart from this, multiple blood transfusions were given.

On day 4, haemoglobin further decreased to 3.9 gm. dL^{-1} with PCV of 0.45 10^9. dL^{-1} (Table 1, Figure 1). PTZ was stopped but metronidazole was continued and imipenem 500 mg every 6 hourly intravenous was added. A gradual improvement in CBC was seen after discontinuing PTZ therapy as evident from haematological and clinical picture of the patient (Table 1). Apart from mechanical ventilation, the patient was managed with ICU supportive management. The hemoglobin increased to 8.4 gm.dL^{-1} with PCV of 0.89 10^9.dL^{-1} and TLC of 3800.mL^{-1} . Patient was successfully extubated on day 9 after gradually weaning off from the ventilatory support and shifted to ward on day 11 of ICU stay on room air with normal haematological investigations.

DISCUSSION

In the present case, besides other management issues, pancytopenia was prominent and developed on day 3 of ICU stay without any obvious cause. The temporal correlation with discontinuation of PTZ and subsequent haematological recovery supports the diagnosis of PTZ induced reversible pancytopenia .

Pancytopenia is characterised by decrease in all three hematopoietic cell lines which is frequently encountered in trauma patients.[1,2] The various causes of pancytopenia are bacterial and viral infections, aplastic anaemia, megaloblastic anaemia, radiation, leukaemia, lymphoma, carcinoma, myeloma, cytotoxic and other drugs such as antibiotics and anticonvulsants, granulomatous diseases such as tuberculosis and sarcoidosis, autoimmune diseases such as systemic lupus erythromatosus, hemophagocytosis.[1,2]

PTZ is a broad spectrum beta-lactam antibiotic of the ureidopenicillin class commonly used in combination with beta-lactamase inhibitor tazobactam against many gram positive and gram negative bacterial infections.[2,3] Some of the known side effects of PTZ are hypersensitivity reactions, hepatotoxicity, neurotoxicity, electrolyte and acid-base disturbances, bleeding disorders and bone marrow suppression which may manifest as neutropenia, thrombocytopenia and rarely haemolytic anaemia.[3-5] These adverse effects have been reported mostly on prolonged therapy (≥ 21 days) due to increased cumulative dosage.[4-6] Beta-lactams are known to cause neutropenia as a complication which is due to the direct toxicity over myeloid precursor cells leading to reversible maturation arrest.[2,3] Anaemia and thrombo-cytopenia are mainly immunologically mediated.[5,6] Bone marrow suppression can generally be seen in postoperative trauma patients, but what prompted to discontinue PTZ in the present case was neutropenia.

The literature reports only a few cases with decreasing CBC mainly seen in a child or an elderly patient within one week of starting therapy with PTZ.[3,4,7] Hypersensitivity responses against drugs such as antibiotics may be more evident in younger patients with no comorbid conditions and due to better immune systems.[6] PTZ caused reversible pancytopenia in the present case even during a brief period of therapy and prompt recovery was seen in the patient after discontinuation of PTZ.

Ethical considerations: No ethical issues involved

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Disclosures: No conflict of interest declared

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Terra firma-forme dermatosis : just a dirty face ?

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ABSTRACT

Terra firma- forme dermatosis is a rare clinical entity which presents as persistent dirt like asymptomatic plaques over the face and neck. These lesions cannot to be removed in spite of normal washing habits of the patient and need to be removed with isopropyl soaked gauze pieces. A case of a 29 year old female presenting with such lesions is being reported and the clinical management is being discussed.

INTRODUCTION

Terra firma-forme dermatosis (TFFD) is a benign, acquired, uncommon disorder of keratinization with a characteristic clinical appearance of brownish to black dirt-like hyperkeratotic plaques or papules over the face and neck. These lesions are resistant to simple washing but can be removed with forceful swabbing with 70% isopropyl alcohol.[1] As dermatitis neglecta and TFFD may have similar clinical manifestations, they are very commonly confused with each other but TFFD's skin lesions cannot be removed by routine bathing habit.[2] A case of this rare dermatosis is being presented.

CASE REPORT

A 29 year old unmarried female presented to the dermatology out-patient department with asymptomatic, persistent brownish-grey dirt-like skin lesions all over her face and neck from the last 5 years (Figure 1a). She gave history of adequate personal hygiene but was not able to clear off the lesions with soap and water. She also complained of matting of hairs over parietal and vertex area (Figure 2a) .

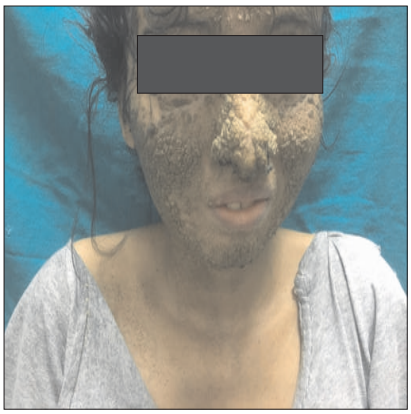

Fig. 1a : Dirty scaly crusted face

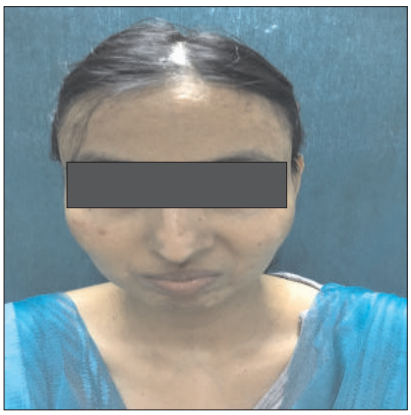

Fig. 1 b : Clearance of face after treatment

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Cutaneous examination revealed brown-grey thick, velvety, reticulated plaques over whole face and neck area. There was matting of hairs with the same dirt like material mainly over the right parietal and vertex area. Pediculosis capitis was ruled out on clinical examination. Initial tentative diagnosis of TFFD and dermatitis neglecta. As the lesions could not be removed with soap and water cleaning, thus dermatitis neglecta was ruled out.

Skin biopsy revealed mild orthokeratosis, hyperkeratosis, focally along with anastomosing rete ridges at places. The papillary dermis showed mild lymphomononuclear infiltrate around blood vessels. Increased melanin pigment was found on Masson Fontana special stain

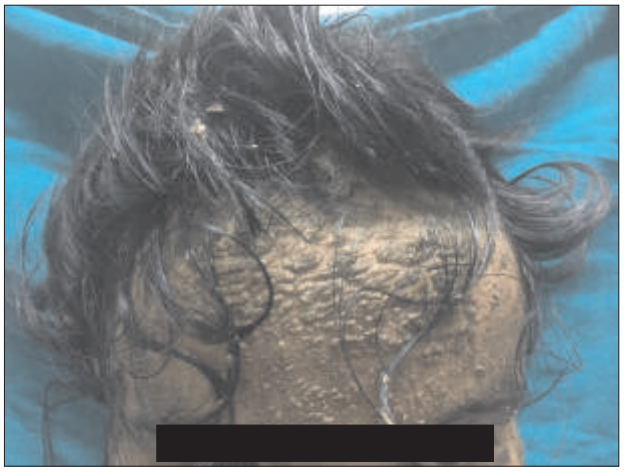

Fig. 2a : Matted hair due to adherent scaling and crusting.

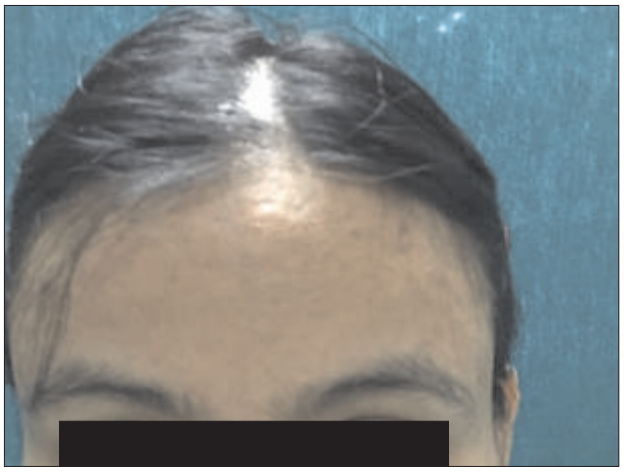

Fig. 2b : Clearance of matted hair after treatment

Along with the patient's general well-being and good cleaning habits, the diagnosis of TFFD was made with a single wipe of the lesions with 70% isopropyl alcohol soaked gauze pieces (Figure 1b and 2b).

The patient was satisfied with the immediate clearance of the lesions and there was no recurrence in 6 months follow up.

DISCUSSION

TFFD is an acquired, benign disorder of keratinization characterized by retention hyperkeratosis presenting as brownish dirt like plaques, first described by Duncan et al in 1987 hence called Duncan's Dirty Dermatosis.[3] The term TFFD has been derived from latin phrase ' terra firma' meaning 'dirty land' because of its presentation as dry dirt like plaques.[4] The plaques may also have a papillomatous or verrucous appearance. TFFD affects all age groups ranging from toddlers to as old as 72 years with equal incidence in both genders. There is no genetic predisposition or familial predominance.[2] The most commonly involved sites are face, neck, trunk or ankles, although unusual sites such as scalp, lips, chest, axilla, back, umbilicus, pubis, arms and legs have also been reported. The distribution can be localised, generalised, unilateral or bilateral.[4]

The exact etiopathogenesis is unknown but it has been attributed to abnormal and delayed keratinization which leads to incomplete keratinocyte maturation and melanin retention. Some reports suggests sunlight as a triggering agent. Erkek et al reported the role of remnant cleansers, soaps, emollients and pathological scaling in diseased skin imparting the skin adhesive and keratoplastic properties at some sites that prevent normal keratinocyte shedding and

accumulates scales, dirt and sebum leading to dirty dermatosis.[5]

TFFD is seen in people with ordinary washing habits, thereby excluding inadequate cleansing as the cause of lesions as seen in dermatitis neglecta. In contrast to dermatitis neglecta, normal cleaning with soap and water cannot remove the plaques but wiping off with isopropyl alcohol is very effective. So history of washing habit is the most important point, as some authors have considered the dermatitis neglecta and TFFD as synonymous. Therefore it is important to know the difference between the two. Other differential diagnosis includes confluent and reticulate papillomatosis of Gougerot, Darier's disease, epidermal nevi, acanthosis nigricans, hyperkeratosis head and neck malassezia dermatosis (HHNMD), dirty neck syndrome of atopic dermatitis, ichthyosis and idiopathic deciduous skin.[4] The diagnosis of TFFD can be confirmed by rubbing forcefully with a gauze piece immersed into 70 percent isopropyl alcohol. This test is both diagnostic as well as therapeutic and it prevents the unnecessary laboratory work up. Biopsy of such cases shows prominent lamellar hyperkeratosis, keratotic plugging of follicular orifices, papilllomatosis, dermal odema, pigment laden macrophages along with perivascular lymphocytic infiltration.[6] Other treatment modalities include chemical peeling with salicylic acid, urea creams, scrub washing with pumice etc. Few patients may require application of isopropyl alcohol weekly to maintain resolution.[7]

TFFD is a rare disorder with very few cases in literature, however this disorder may be more common than literature as it could be mis-diagnosed and underreported. TFFD may cause anxiety, discomfort and embarrassment in the patints owing to its appearance. In order to avoid costly and exhaustive endocrinological evaluation, it is important to be aware of this rare entity.

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Disclosures: No conflict of interest declared

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2. **Books and other monographs**

   Personal author(s)

   Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

   Chapter in a book

   Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

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