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# From the Editor



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In this issue of the journal two papers discussed the problem of atherosclerotic lesions in sickle cell disease. In the first paper the authors attempted to understand whether or not there is an atherosclerotic background of hepatomegaly, left lobe hypertrophy, and cirrhosis in sickle cell diseases (SCDs). All patients with the SCDs were included into the study. The study included 434 patients (222 males). Mean ages were similar in males and females (30.8 versus 30.3 years, respectively,  $P>0.05$ ). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males ( $P<0.001$  for both). Although the relatively younger mean ages, the prevalence of hepatomegaly (59.4%), left lobe hypertrophy (7.1%), cirrhosis (5.0%) were very high. On the other hand, transfused units of red blood cells in their lives (48.1 versus 28.5,  $P=0.000$ ), chronic obstructive pulmonary disease (25.2% versus 7.0%,  $P<0.001$ ), ileus (7.2% versus 1.4%,  $P<0.001$ ), cirrhosis (8.1% versus 1.8%,  $P<0.001$ ), leg ulcers (19.3% versus 7.0%,  $P<0.001$ ), digital clubbing (14.8% versus 6.6%,  $P<0.001$ ), coronary artery disease (18.0% versus 13.2%,  $P<0.05$ ), chronic renal disease (9.9% versus 6.1%,  $P<0.05$ ), and stroke (12.1% versus 7.5%,  $P<0.05$ ) were all higher in males. The authors concluded that SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Although the relatively younger mean ages, the very high prevalence of hepatomegaly, left lobe hypertrophy, and cirrhosis are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at the arterial and venous systems of the liver, and the left lobe hypertrophy may be a progression step between hepatomegaly and cirrhosis in the SCDs.

In the second paper the authors tried to understand whether or not there is an atherosclerotic background of benign prostatic hyperplasia in the SCDs patients. They stressed that Sickle cell diseases (SCDs) are accelerated atherosclerotic processes.

The study included 428 patients (220 males). The mean ages were similar in males and females (30.6 versus 30.1 years, respectively,  $P>0.05$ ). Smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were significantly higher in males ( $P<0.001$  for both). Transfused units of red blood cells in their lives (47.6 versus 28.4,  $P=0.000$ ), chronic ob-

structive pulmonary disease (25.4% versus 7.2%,  $P<0.001$ ), ileus (7.2% versus 1.4%,  $P<0.001$ ), cirrhosis (7.7% versus 1.9%,  $P<0.001$ ), leg ulcers (20.0% versus 7.2%,  $P<0.001$ ), digital clubbing (14.0% versus 6.2%,  $P<0.001$ ), coronary artery disease (18.1% versus 12.9%,  $P<0.05$ ), chronic renal disease (10.4% versus 6.2%,  $P<0.05$ ), and stroke (12.2% versus 7.6%,  $P<0.05$ ) were all higher in males, too. There were 11 males (5.0%) with lower urinary tract symptoms (LUTS) including urgency, weak stream, incomplete emptying, and nocturia with a mean age of 41.4 years. All patients could be treated with once daily 4 milligrams of doxazosin, orally. The authors concluded that SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Although the relatively younger mean age of the patients, LUTS are probably due to the disseminated endothelial damage, inflammation, edema, and fibrosis both in the arterial and venous systems of the prostate in the SCDs.

A retrospective study paper from Egypt present the challenges encountered in the diagnosis and treatment of GIST cases in our facility Saudi German Hospital Riyadh Saudi Arabia during the past 10 years and compare the results obtained with that of other oncology centers. This study is a retrospective study of cases with GIST that diagnosed and treated in our center during the past 10 years. These studies include clinical characteristics, target therapy, imaging techniques, histopathology, immunohistochemistry, surgical techniques and prognosis of such cases. A total of thirty two patients were diagnosed as having GIST (24 males/8 females) with a mean age 62 years (31-83 years). Diagnosis was made preoperatively in 22 patients (69%) and intraoperatively with histopathological confirmation in ten patients (31%). The site of the tumor was detected in the stomach in twelve cases (37.5%), two in duodenum (6.25%), ten in small intestine (31.25%), two in mesentery (6.25%), four in colon (12.5%) and two rectal GIST (6.25%). The main presentation of the disease was anemia, GIT bleeding and abdominal mass. Twenty eight patients considered resectable and they were operated upon (87.5%) and in four patients (12.5%) neoadjuvant therapy was started with favorable response in two cases and poor response in other two with advanced GIST. All patients received Imatinib as adjuvant therapy. Mean follow up period was 33 months (4-54 months). The authors concluded that GIST is a challenging malignant tumor that requires a multidisciplinary approach in a highly specialized facility seeking for the best management and prognosis.

A retrospective study from Yemen looked at the descriptive patterns of findings seen in hysterectomy specimens based on records from Modern - histopathology laboratory in Aden. A total of 2544 specimens were analyzed during the 6 years period from January 2006 to December 2012, to study the histopathological findings of these specimens. The age of the patients at hysterectomy ranged from 16-80 years with a mean of 44.6, maximum patients (56.3%) in the age group 41-50 years and less patients in less than 30 years. Most common pathology findings are, Endometrial hyperplasia 1481 (58.3%), Non neoplastic cystic lesion 1386 (54.5%), Chronic cervicitis 1363 (53.6%), Adenomyosis 793 (31.2%) follow by Leiomyomas 697 (27.4%). Other less frequent pathologies identified included atrophic endometrium, Inadequate secretory endometrial transformation, Gestational Trophoblastic disease, Endometroid adenocarcinoma, cervical prolapse. The authors concluded that the study confirms that benign pathologies are more common in hysterectomy specimens than their malignant counterparts.

A review paper looked at Progressive Ataxia of Unknown Etiology. The hereditary ataxias are a heterogeneous group of diseases. Most attempts at classification have been based on pathologic findings and are not always useful for the clinicians. Many of these disorders are multisystem degeneration in which the underlying biochemical or other defect is usually unknown. The pathophysiology is correspondingly poorly understood. Hereditary ataxia can be divided into the hereditary congenital ataxia, the ataxia linked with metabolic disorder, and early onset ataxia of unknown etiology.

# Atherosclerotic background of benign prostatic hyperplasia in sickle cell diseases

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## ABSTRACT

**Background:** Sickle cell diseases (SCDs) are accelerated atherosclerotic processes. We tried to understand whether or not there is an atherosclerotic background of benign prostatic hyperplasia in the SCDs patients.

**Methods:** All patients with the SCDs were included into the study.

**Results:** The study included 428 patients (220 males). The mean ages were similar in males and females (30.6 versus 30.1 years, respectively,  $P>0.05$ ). Smoking (24.0% versus 6.2%) and alcohol (5.0% versus 0.4%) were significantly higher in males ( $P<0.001$  for both). Transfused units of red blood cells in their lives (47.6 versus 28.4,  $P=0.000$ ), chronic obstructive pulmonary disease (25.4% versus 7.2%,  $P<0.001$ ), ileus (7.2% versus 1.4%,  $P<0.001$ ), cirrhosis (7.7% versus 1.9%,  $P<0.001$ ), leg ulcers (20.0% versus 7.2%,  $P<0.001$ ), digital clubbing (14.0% versus 6.2%,  $P<0.001$ ), coronary artery disease (18.1% versus 12.9%,  $P<0.05$ ), chronic renal disease (10.4% versus 6.2%,  $P<0.05$ ), and stroke (12.2% versus 7.6%,  $P<0.05$ ) were all higher in males, too. There were 11 males (5.0%) with lower urinary tract symptoms (LUTS) including urgency, weak stream, incomplete emptying, and nocturia with a mean age of 41.4 years. All patients could be treated with once daily 4 milligrams of doxazosin, orally.

**Conclusion:** SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Although the relatively younger mean age of the patients, LUTS are probably due to the disseminated endothelial damage, inflammation, edema, and fibrosis both in the arterial and venous systems of the prostate in the SCDs.

**Key words:** Sickle cell diseases, chronic endothelial damage, atherosclerosis, benign prostatic hyperplasia

## Introduction

Chronic endothelial damage is the leading cause of aging, morbidity, and mortality by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent injuries on endothelium. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are physical inactivity induced weight gain, smoking, alcohol consumption, and other chronic inflammatory processes including sickle cell diseases (SCDs), rheumatologic disorders, chronic infections, and cancers for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging, morbidity, and mortality. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may prevent terminal endpoints, after development of obesity, HT, DM, cirrhosis, PAD, COPD, CRD, CAD, or stroke, endothelial changes can not be reversed completely due to their fibrotic natures (3). Benign prostatic hyperplasia (BPH) is also found among one of the most frequent health problems in men above the age of 50 years and its prevalence is progressively increased by aging. We tried to understand whether or not there is an atherosclerotic background of BPH in the SCDs patients in the present study.

## Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and April 2016. All patients with the SCDs were included into the study. The SCDs are diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking habit, regular alcohol consumption, painful crises per year, transfused units of red blood cells (RBCs) in their lives, surgical operations, leg ulcers, stroke, priapism, and lower urinary tract symptoms (LUTS) including urgency, weak stream, incomplete emptying, and nocturia were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a

Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (4). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (5). CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL in males and 1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, ultrasonographic evaluation, and tissue samples in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (6, 7). An exercise electrocardiogram is performed just in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the exercise electrocardiogram positive cases. So CAD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Avascular necrosis of bone is diagnosed by means of MRI (8). Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually male and female patients were collected into the two groups, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 428 patients with the SCDs (208 females and 220 males). Mean ages of the patients were similar in males and females (30.6 versus 30.1 years, respectively,  $P>0.05$ ). Prevalence of associated thalassemia minors were similar in males and females, too (72.2% versus 67.7%, respectively,  $P>0.05$ ). Smoking (24.0% versus 6.2%) and alcohol consumption (5.0% versus 0.4%) were significantly higher in males ( $P<0.001$  for both) (Table 1). Transfused units of RBCs in their lives (47.6 versus 28.4,  $P=0.000$ ), COPD (25.4% versus 7.2%,  $P<0.001$ ), ileus (7.2% versus 1.4%,  $P<0.001$ ), cirrhosis (7.7% versus 1.9%,  $P<0.001$ ), leg ulcers (20.0% versus 7.2%,  $P<0.001$ ), digital clubbing (14.0% versus 6.2%,  $P<0.001$ ), CAD (18.1% versus 12.9%,  $P<0.05$ ), CRD (10.4% versus 6.2%,  $P<0.05$ ), and stroke (12.2% versus 7.6%,  $P<0.05$ ) were all higher in males, significantly. There were two cases with sickle cell retinopathy in males and two in females (0.9% versus 0.9%,  $P>0.05$ ). There were 30 mortality cases (16 males) during the ten-year follow-up period.

Table 1: Characteristic features of the study cases

Variables	Male patients with SCDs*	P-value	Female patients with SCDs
Prevalence	51.4% (220)	Ns†	48.5% (208)
Mean age (year)	30.6 ± 10.1 (5-58)	Ns	30.1 ± 9.9 (8-59)
Thalassemia minors	72.2% (159)	Ns	67.7% (141)
<u>Smoking</u>	<u>24.0% (53)</u>	<u>&lt;0.001</u>	<u>6.2% (13)</u>
<u>Alcoholism</u>	<u>5.0% (11)</u>	<u>&lt;0.001</u>	<u>0.4% (1)</u>

\*Sickle cell diseases †Nonsignificant (P>0.05)

Table 2: Associated pathologies of the study cases

Variables	Male patients with SCDs*	P-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
<u>Transfused RBC‡ units</u>	<u>47.6 ± 61.6 (0-434)</u>	<u>0.000</u>	<u>28.4 ± 35.8 (0-206)</u>
<u>COPD§</u>	<u>25.4% (56)</u>	<u>&lt;0.001</u>	<u>7.2% (15)</u>
<u>Ileus</u>	<u>7.2% (16)</u>	<u>&lt;0.001</u>	<u>1.4% (3)</u>
<u>Cirrhosis</u>	<u>7.7% (17)</u>	<u>&lt;0.001</u>	<u>1.9% (4)</u>
<u>Leg ulcers</u>	<u>20.0% (44)</u>	<u>&lt;0.001</u>	<u>7.2% (15)</u>
<u>Digital clubbing</u>	<u>14.0% (31)</u>	<u>&lt;0.001</u>	<u>6.2% (13)</u>
<u>CAD¶</u>	<u>18.1% (40)</u>	<u>&lt;0.05</u>	<u>12.9% (27)</u>
<u>CRD**</u>	<u>10.4% (23)</u>	<u>&lt;0.05</u>	<u>6.2% (13)</u>
<u>Stroke</u>	<u>12.2% (27)</u>	<u>&lt;0.05</u>	<u>7.6% (16)</u>
Pulmonary hypertension	12.7% (28)	Ns	12.5% (26)
Varices	8.6% (19)	Ns	5.7% (12)
Rheumatic heart disease	6.8% (15)	Ns	5.7% (12)
Avascular necrosis of bones	25.0% (55)	Ns	25.0% (52)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Mortality	7.2% (16)	Ns	6.7% (14)

\*Sickle cell diseases †Nonsignificant (P>0.05) ‡Red blood cell §Chronic obstructive pulmonary diseases ¶Coronary artery disease \*\*Chronic renal disease

The mean ages of mortality were 30.8 ± 8.3 years (range 19-50) in males and 33.3 ± 9.2 years (range 19-47) in females (P>0.05) (Table 2). On the other hand, there were 11 males (5.0%) with LUTS with a mean age of 41.4 ± 10.6 (27-58) years. All of the patients could be treated with once daily 4 milligrams of doxazosin, orally. Additionally, there were 22 cases (10.0%) with priapism with a mean age of 33.3 ± 8.1 (18-51) years.

## Discussion

SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failure in early years of life. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of RBCs. Probably loss of elasticity instead of shape is the main problem since sickling is very rare in peripheral blood samples of cases with associated thalassemia minors, and human survival is not so affected in

hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with increased metabolic rate of the body. The hard RBCs induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated cellular hypoxia all over the body (9, 10). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (11, 12), since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (13), whereas they were 33.3 and 30.8 years in the present study, respectively. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during severe medical or surgical events in Antakya region. Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCDs (14, 15). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBCs. So it decreases sickling and sickling induced endothelial damage and inflammation all over the body. According to our ten-year observations, simple transfusions are superior to exchange. First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or higher gives time to clinicians to prepare more units by preventing sudden death of such individuals. Secondly, transfusion of one or two units of RBC suspensions in each time decreases the severity of pain and relaxes anxiety of the patients and their families in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions in each time will decrease transfusion-related complications in the future. Fourthly, transfusion of RBC suspensions in secondary health centers may prevent some deaths developed during transport to tertiary centers for the exchange. On the other hand, longer lifespan of females with the SCDs (13) and longer overall survival of females in general (16) cannot be explained by the atherosclerotic effects of smoking or alcohol alone, instead it may be explained by higher physical and emotional stresses of male sex that may terminate with an exaggerated atherosclerosis and sickling induced atherosclerosis all over the body (17).

BPH rather than hypertrophy is the most common benign neoplasm in men. Although prostate specific antigen (PSA) may be elevated in these patients because of increased organ volume and inflammation secondary to urinary tract infections, BPH does not lead to cancer. BPH involves hyperplasia of stromal and epithelial cells, terminating with the formation of large, commonly discrete nodules in the transition zone of the gland. When sufficiently large, the nodules apply pressure on the urethra and increase resistance to urinary flow. This is commonly felt as obstruction, although the urethral lumen is only compressed. Resistance to urinary flow requires the bladder to work stronger during voiding, possibly leading to progressive hypertrophy, instability, and atony of bladder muscle. BPH can be diagnosed by using the UWIN score (urgency, weak stream, incomplete emptying, and nocturia) (18). BPH may be caused by failure of the spermatic venous system result-

ing with increased hydrostatic pressure and testosterone levels, locally (19). Authors found that the one-way valves in the vertically oriented internal spermatic veins are destroyed in BPH patients causing elevated hydrostatic pressure up to 6-fold greater than the normal (19). The elevated pressure propagates to all interconnected vessels leading to a venous flow retrograde from higher pressure of the testicular veins to lower pressure of the prostate. They have found that free testosterone levels in this blood are elevated up to 130-fold above the serum (19). Consequently, the prostate is exposed both to an increased venous pressure that causes hypertrophy and to an elevated free testosterone level causing hyperplasia. On the other hand, an age-related impairment of blood supply to the gland may also have a key role in the development of BPH (20). An advanced atherosclerosis in elder men may cause chronic tissue hypoxia, and thus be a contributing factor in the pathogenesis (21). Smooth muscle proliferation may be an important and possibly androgen-dependent step in the development of atherosclerosis and BPH (22). Similarly, there was a larger prostate in men with type 2 DM ( $P=0.0058$ ), HT ( $P=0.0317$ ), obesity ( $P<0.0001$ ), and low high density lipoprotein (HDL)-cholesterol ( $P=0.0132$ ) and high insulin levels ( $P<0.0001$ ) (23). The gland volume correlated positively with the systolic BP ( $P=0.03$ ), obesity ( $P<0.0001$ ), and fasting insulin ( $P<0.0001$ ) and negatively with HDL-cholesterol levels ( $P=0.009$ ) (23). As already known, they were significant components of the metabolic syndrome that is the accelerated atherosclerotic process all over the body (23). Similarly, frequency of CAD was 9% and 29% in men with PSA levels below and above 1.0 microgram/L, respectively ( $P<0.03$ ) (22). These results may suggest that BPH may be one of the terminal endpoints of accelerated atherosclerotic process in the body.

Varices are abnormally dilated vessels with tortuous courses. They usually occur in the venous system of the legs. Related factors include pregnancy, obesity, menopause, aging, and heredity. In other words, varices are more frequent with female sex and components of the metabolic syndrome. Interestingly, although the younger mean ages of the patients (30.6 years in males and 30.1 years in females) in the present study and significantly lower body mass index (BMI) of the SCDs cases in the literature (4), deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were higher among the study cases (8.6% in males and 5.7% in females,  $P>0.05$ ). Normally, leg muscles pump veins to return blood to heart against gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination should be performed in upright position. Deep venous thrombosis is another possible cause of varicose veins. Severe long-standing varicose veins can lead to leg swelling, venous eczema, skin thickening, and ulcerations, but life-threatening complications are rare. Although the relatively younger mean age of the study cases and significantly lower BMI of the SCDs cases in the literature (4), the high prevalences of deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs (7.2%) may show an additional venous endothelial involvement in the SCDs.

Priapism is the painful erection of penis that does not return to its flaccid state within four hours in the absence of any stimulation (24). Damage to vascular endothelium may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, non-erectile penis (24). Ninety-five percent of clinically presented priapisms are veno-occlusive (low flow) type in which blood does not return adequately from the penis as in the SCDs. The other 5% are arterial (high flow) type usually caused by a blunt perineal trauma in which there is a short-circuit of the vascular system (24). Treatment of arterial type is not as urgent as that of venous type since there is no risk of ischemia (24). Oral pseudoephedrine or terbutaline may relax the stretched corporeal smooth muscles and increase permeability of erectile cavernous tissue that may permit easy flow of fluid from sinusoids into the venous system. If the drugs are not effective, aspiration of blood from the corpus cavernosum under local anesthesia is tried. If the aspiration also fails, distal shunts may cause the blood to leave the penis. Whereas in the SCDs, RBC support should be the treatment of choice in acute phase (25). RBC transfusions decrease sickle cell concentration in blood, suppress the bone marrow in production of abnormal RBCs, and eventually prevent further sickling induced damage to the penis. Whereas in chronic phase, hydroxyurea should be the treatment of choice in priapism in the SCDs. It is the only drug that was approved by Food and Drug Administration for the treatment of SCDs (11). It is an oral, cheap, safe, and highly effective drug for the SCDs that blocks cell division by suppressing formation of deoxyribonucleotides which are building blocks of DNA (12). Its main action may be suppression of hyperproliferative WBCs and PLTs in the SCDs (26). Although presence of continuous damage of hard RBCs particularly on capillary endothelium, severity of the destructive process is probably exaggerated by the patients' own WBCs and PLTs as in the autoimmune disorders. Similarly, lower neutrophil counts were associated with lower crises rates, and if a tissue infarct occurs, lower neutrophil counts may decrease severity of pain and tissue damage (27). According to our observations, hydroxyurea is an effective drug for prevention of attacks of priapism and its terminal consequences if initiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls later in life.

COPD is the third leading cause of mortality in the world (28). It is an inflammatory disorder mainly affecting the pulmonary vasculature, and physical inactivity induced weight gain, smoking, and aging may be the major causes. Probably regular alcohol consumption also takes a role in the inflammatory process. For example, both prevalence of alcohol consumption and COPD were significantly higher in males in the present study ( $P < 0.001$  for both). Similarly, COPD was one of the most frequent associated disorders in alcohol dependence in another study (29). Additionally, 30-day readmission rate to the hospitals was higher in COPD patients with alcoholism (30). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The endothelial process is enhanced by release of various chemicals by inflammatory cells, and terminates with endothelial fibrosis and tissue losses in the lungs. Although COPD may mainly be thought as an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of a disseminated endothelial inflammation

all over the body, and close relationships were observed between COPD, CAD, PAD, and stroke (31, 32). Two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in smokers, and when the hospitalizations were researched, the most common causes were the cardiovascular diseases again (33). Similarly, 27% of mortalities were due to the cardiovascular causes in the moderate and severe COPD cases in another study (34). Due to the strong atherosclerotic natures of the SCDs and COPD, COPD may be one of the terminal endpoints of the SCDs due to the higher prevalences of priapism, leg ulcers, clubbing, CAD, CRD, and stroke in the COPD group in another study (35).

Smoking has major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CAD, stroke, and cancers (36). Its atherosclerotic effects are the most obvious in COPD and Buerger's disease. Buerger's disease has never been reported in the absence of smoking in the literature. Smoking induced endothelial damage is probably seen in pulmonary vasculature much more than the other organs due to the higher concentrations of its products, here. But smoking may even cause cirrhosis, CRD, PAD, CAD, stroke, and cancers by the transport of its products within the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. On the other hand, beside the strong atherosclerotic effects, smoking in human beings and nicotine in animals may be associated with some weight loss (37). There may be increased energy expenditure during smoking (38), and nicotine may decrease caloric intake in a dose-related manner (39). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (40). Similarly, BMI seems to be the highest in the former and the lowest in the current smokers (41). As a pleasure in life, smoking may also show the weakness of volition to control eating. For example, prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (42). Additionally, although CAD was detected with similar prevalence in both sexes, smoking and COPD were higher in males against the higher prevalence of BMI and its terminal consequences including dyslipidemia, HT, and DM in females (36). Probably toxic substances of tobacco smoke cause a diffuse inflammation on vascular endothelium all over the body, and it is the major cause of loss of appetite during circulation of the substances within the blood, since the body can't eat anything during fighting. So regular smoking comes with a prominent weight loss in front of us, clinically. On the other hand, when we considered some antidepressant properties of smoking and alcohol, the higher prevalences of them may also show higher stresses and shortened survival in males.

Digital clubbing should alert physicians about some systemic disorders in the body (10). It is characterized by loss of normal  $<165^\circ$  angle between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (43). Some authors detected clubbing in 0.9% of all patients admitted to the department of internal medicine (7), whereas the prevalence was 4.2% in the same department in our university (10). The exact cause and significance is unknown but chronic tissue hypoxia has been proposed (44). In the above study, only 40% of clubbing cases turned out to have significant underlying

diseases while 60% remained well over the subsequent years (7). But according to our observations, digital clubbing is frequently associated with pulmonary, cardiac, and/or hepatic disorders or smoking that are featuring with chronic tissue hypoxia. As an explanation for that lungs, heart, and liver are closely related organs that affect their functions in a short period of time. Similarly, digital clubbing may be an indicator of disseminated atherosclerosis at the capillary level in the SCDs, and we observed clubbing in 10.2% of patients with the SCDs in the present study. Beside the effects of SCDs, the higher prevalences of smoking, COPD, and clubbing in males ( $P < 0.001$  for all) may also show some additional roles of smoking, COPD, and male sex on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (45), and the ratio was 13.7% in the present study. Its incidence increases with age, male sex, and HbSS genotype (45). Similarly, its ratio was higher in males (20.0% versus 7.2%,  $P < 0.001$ ), and mean age of the patients with leg ulcers was higher than the others (35.1 versus 29.6 years,  $P < 0.000$ ), here. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (46). As an evidence of their atherosclerotic background, the leg ulcers occur in distal areas with less collateral blood flow in the body (46). The hard RBCs induced chronic endothelial damage at the capillary level may be the major cause in the SCDs (45). Prolonged exposure to the hard bodies due to blood pooling in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The hard RBCs induced venous insufficiencies may also accelerate the process by pooling of causative hard bodies in the legs, and vice versa. Pooling of blood in the lower extremities may also have some effects on the venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Beside the hard bodies, smoking and alcohol may also have some effects on the leg ulcers since both of them are more common in males, and their atherosclerotic effects are obvious in COPD, Buerger's disease, and cirrhosis (45). According to our ten-year observations, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to increased WBC and PLT counts induced prolonged endothelial inflammation and edema at the capillary level in the SCDs.

Stroke is also a common complication of the SCDs (47). Similar to acute chest syndrome (ACS) and leg ulcers, it is more common with the HbSS genotype and with a higher WBC count (26, 48). Sickling induced disseminated endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain (26). Stroke may not have a macrovascular origin, instead generalized endothelial inflammation and edema at the capillary level may be much more important in the SCDs. Infections, serious injuries, inflammatory disorders, and other stresses may precipitate the stroke since increased metabolic rate during such events may accelerate sickling and secondary endothelial inflammation and edema even in the brain. Similar to the ACS and leg ulcers, a significant reduction with hydroxyurea may also suggest that a significant proportion of stroke is secondary to increased WBC and PLT counts induced disseminated endothelial inflammation and edema in the brain in the SCDs (49).

As a conclusion, SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failure in early years of life. Although the relatively younger mean age of the patients, LUTS are probably due to the disseminated endothelial damage, inflammation, edema, and fibrosis both in the arterial and venous systems of the prostate in the SCDs.

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# Atherosclerotic background of hepatomegaly, left lobe hypertrophy, and cirrhosis in sickle cell diseases

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## ABSTRACT

**Background:** We tried to understand whether or not there is an atherosclerotic background of hepatomegaly, left lobe hypertrophy, and cirrhosis in sickle cell diseases (SCDs).

**Methods:** All patients with the SCDs were included into the study.

**Results:** The study included 434 patients (222 males). Mean ages were similar in males and females (30.8 versus 30.3 years, respectively,  $P>0.05$ ). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males ( $P<0.001$  for both). Although the relatively younger mean ages, the prevalence of hepatomegaly (59.4%), left lobe hypertrophy (7.1%), cirrhosis (5.0%) were very high. On the other hand, transfused units of red blood cells in their lives (48.1 versus 28.5,  $P=0.000$ ), chronic obstructive pulmonary disease (25.2% versus 7.0%,  $P<0.001$ ), ileus (7.2% versus 1.4%,  $P<0.001$ ), cirrhosis (8.1% versus 1.8%,  $P<0.001$ ), leg ulcers (19.3% versus 7.0%,  $P<0.001$ ), digital clubbing (14.8% versus 6.6%,  $P<0.001$ ), coronary artery disease (18.0% versus 13.2%,  $P<0.05$ ), chronic renal disease (9.9% versus 6.1%,  $P<0.05$ ), and stroke (12.1% versus 7.5%,  $P<0.05$ ) were all higher in males.

**Conclusion:** SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failure in early years of life. Although the relatively younger mean ages, the very high prevalence of hepatomegaly, left lobe hypertrophy, and cirrhosis are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at the arterial and venous systems of the liver, and the left lobe hypertrophy may be a progression step between hepatomegaly and cirrhosis in the SCDs.

**Key words:** Sickle cell diseases, chronic endothelial damage, atherosclerosis, hepatomegaly, left lobe hypertrophy, cirrhosis

## Introduction

Chronic endothelial damage may be the leading cause of aging-induced morbidities and mortalities by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic natures that reduce blood flow and increase systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are physical inactivity induced weight gain, smoking, alcohol, and other chronic inflammatory or infectious processes including sickle cell diseases (SCDs), rheumatologic disorders, tuberculosis, and cancers for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary artery disease (CAD), mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging-induced morbidities and mortalities. They were discussed under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, after development of obesity, HT, DM, PAD, COPD, CRD, CAD, or stroke, the endothelial changes cannot be reversed completely due to their fibrotic nature (3). Similarly, cirrhosis is also a progressively increasing cause of morbidity and mortality in the world (4), and it may also be one of the terminal consequences of the systemic atherosclerotic process. We tried to understand whether or not there is an atherosclerotic background of hepatomegaly, left lobe hypertrophy, and cirrhosis in the SCDs.

## Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCDs were included into the study. The SCDs are diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of red blood cells (RBCs) in their lives, surgical operations, leg ulcers, stroke, priapism, and lower urinary tract symptoms (LUTS) in males including urgency, weak stream, incomplete emptying, and nocturia, were learnt. Due to their cumulative atherosclerotic effects together with the SCDs, patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same internist. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and

valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones were scanned for avascular necrosis according to the patients' complaints. So avascular necrosis of bone was diagnosed by means of MRI (5). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (6). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (8, 9). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CAD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the computed tomography of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually prevalences of hepatomegaly, left lobe hypertrophy, and cirrhosis were detected among all, and male and female patients with the SCDs were compared according to the terminal endpoints in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

The study included 434 patients with the SCDs (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, respectively,  $P>0.05$ ). Prevalence of associated thalassemia minors were similar in males and females too, (72.5% versus 67.9%, respectively,  $P>0.05$ ). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were significantly higher in males ( $P<0.001$  for both) (**Table 1**). Although the relatively younger mean ages of the patients, the prevalence of hepatomegaly (59.4%), left lobe hypertrophy (7.1%), and cirrhosis (5.0%) were very high (**Table 2**). On the other hand, transfused units of RBCs in their lives (48.1 versus 28.5,  $P=0.000$ ), COPD (25.2% versus 7.0%,  $P<0.001$ ), ileus (7.2% versus 1.4%,  $P<0.001$ ), cirrhosis (8.1% versus 1.8%,  $P<0.001$ ), leg ulcers (19.8% versus 7.0%,  $P<0.001$ ), digital clubbing (14.8% versus 6.6%,  $P<0.001$ ), CAD (18.0% versus 13.2%,  $P<0.05$ ), CRD (9.9% versus 6.1%,  $P<0.05$ ), and stroke (12.1% versus 7.5%,  $P<0.05$ ) were all higher in males, significantly. There were 11 males (4.9%) with LUTS with a mean age of  $41.5 \pm 10.6$  (27-58) years. All of the patients could be treated

with once daily 4 milligrams of doxazosin, orally. Additionally, there were 23 cases (10.3%) with priapism with a mean age of  $33.4 \pm 7.9$  (18-51) years. There were two cases with sickle cell retinopathy in males and two in females (0.9% versus 0.9%,  $P>0.05$ ). There were 31 mortality cases (17 males and 14 females) during the ten-year period. The mean ages of mortality were  $30.2 \pm 8.4$  years (range 19-50) in males and  $33.3 \pm 9.2$  years (range 19-47) in females ( $P>0.05$ ) (Table 3).

## Discussion

SCDs are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failure in early years of life. Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of RBCs. Probably loss of elasticity instead of shape is the main pathology since sickling is very rare in peripheral blood samples of cases with associated thalassemia minors, and human survival is not so affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with infections, inflammation, and other stresses of the body. The hard RBCs induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated cellular hypoxia all over the body (10, 11). As a difference from other causes of chronic endothelial damage, the SCDs may keep vascular endothelium particularly at the capillary level (12), since the capillary system is the main distributor of the hard RBCs into the tissues. The hard cells induced chronic endothelial damage builds up an advanced atherosclerosis in younger ages of the patients. As a result, mean lifespans of the patients were 48 years in females and 42 years in males in the literature (13), whereas they were 33.3 and 30.2 years in the present study, respectively. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea, and inadequate RBC supports during emergencies in Antakya region (14). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCDs (15). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow about the production of abnormal RBCs. So it decreases sickling-induced endothelial damage and inflammation all over the body.

Varices are abnormally dilated veins with tortuous courses, and they usually occur in the legs. Their related factors include pregnancy, obesity, menopause, aging, and heredity. In other words, varices are more common in females and in cases with metabolic syndrome. Normally, leg muscles pump veins to return blood against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. Deep venous thrombosis may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination should be performed in upright position. Although the younger mean ages of the patients in the present study (30.8 years in males and 30.3 years in females) and significantly lower body mass index (BMI) of the SCDs cases in the literature (11), deep venous thrombosis and/or varices and/or telangiectasias of the lower limbs were higher among the study cases (9.0% in males and 6.6% in females,

$P>0.05$ ) indicating an additional venous endothelial involvement in the SCDs.

Both the frequency and complications of cirrhosis are increasing in the world. For instance, it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (4). Although the achieved development of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by aging of the human being and increased frequency of excess weight in the world. For instance, non-alcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even in children and adolescents at the moment (16, 17). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (16). NAFLD shares many features of the metabolic syndrome. Besides terminating with cirrhosis, NAFLD is associated with a higher overall mortality as well as with an increased prevalence of cardiovascular diseases (17). Authors have reported independent associations between NAFLD, impaired flow-mediated vasodilation, and increased carotid intima-media thickness (17, 18). NAFLD and cirrhosis may be considered as the hepatic consequences of the systemic accelerated atherosclerotic process, and hepatic fat is highly correlated with parameters of the metabolic syndrome (19). Probably smoking also takes a role in the endothelial inflammatory process in the liver, since the systemic inflammatory effects of smoking on endothelial cells is already known with Buerger's disease and COPD (20). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic accelerated atherosclerotic process in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the higher concentrations of its metabolites in the liver. Similarly, aging alone may be another cause of systemic atherosclerotic process that prevents adequate tissue oxygenation. Chronic infectious or inflammatory diseases may also terminate with an accelerated atherosclerotic process (21). For example, chronic HCV infection had raised carotid intima-media thickness, and normalisation of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (21). Similarly, beside the COPD, ileus, leg ulcers, digital clubbing, CAD, CRD, and stroke, cirrhosis may also be one of the terminal endpoints of the SCDs.

COPD is the third leading cause of mortality in the world (22). It is an inflammatory disorder mainly affecting the pulmonary vasculature, and it may also be called cirrhosis of the lungs. Physical inactivity induced weight gain, smoking, and aging may be the major underlying causes. Probably alcohol also takes a role in the inflammatory process. For example, both prevalence of alcohol and COPD were significantly higher in males in the present study ( $P<0.001$  for both). Similarly, COPD was one of the most frequent associated disorders in alcohol dependence in another study (23). Additionally, 30-day re-admission rates were higher in COPD patients with alcoholism (24). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The endothelial process is enhanced by release of various chemicals by inflam-

Table 1: Characteristic features of the study cases

Variables	Male patients with SCDs*	P-value	Female patients with SCDs
Prevalence	51.4% (220)	Ns†	48.5% (208)
Mean age (year)	30.6 ± 10.1 (5-58)	Ns	30.1 ± 9.9 (8-59)
Thalassemia minors	72.2% (159)	Ns	67.7% (141)
<b>Smoking</b>	<b>24.0% (53)</b>	<b>&lt;0.001</b>	<b>6.2% (13)</b>
<b>Alcoholism</b>	<b>5.0% (11)</b>	<b>&lt;0.001</b>	<b>0.4% (1)</b>

\*Sickle cell diseases †Nonsignificant (P>0.05)

Table 2: Prevalences of hepatomegaly, left lobe hypertrophy, and cirrhosis

Variables	Hepatomegaly	P-value	Left lobe hypertrophy	P-value	Cirrhosis	P-value*
Prevalence	59.6% (259)		7.1% (31)		5.0% (22)	
Male ratio	53.6% (139)		64.5% (20)		81.8% (18)	
<b>Mean age</b>	<b>30.2 ± 9.5 (5-59)</b>	<b>Ns†</b>	<b>33.4 ± 10.7 (19-56)</b>	<b>Ns</b>	<b>37.0 ± 11.5 (19-56)</b>	<b>0.007</b>

\*Sickle cell diseases †Nonsignificant (P>0.05)

Table 3: Associated pathologies of the study cases

Variables	Male patients with SCDs*	P-value	Female patients with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
<b>Transfused RBC‡ units</b>	<b>47.6 ± 61.6 (0-434)</b>	<b>0.000</b>	<b>28.4 ± 35.8 (0-206)</b>
<b>COPD§</b>	<b>25.4% (56)</b>	<b>&lt;0.001</b>	<b>7.2% (15)</b>
<b>Ileus</b>	<b>7.2% (16)</b>	<b>&lt;0.001</b>	<b>1.4% (3)</b>
<b>Cirrhosis</b>	<b>7.7% (17)</b>	<b>&lt;0.001</b>	<b>1.9% (4)</b>
<b>Leg ulcers</b>	<b>20.0% (44)</b>	<b>&lt;0.001</b>	<b>7.2% (15)</b>
<b>Digital clubbing</b>	<b>14.0% (31)</b>	<b>&lt;0.001</b>	<b>6.2% (13)</b>
<b>CAD¶</b>	<b>18.1% (40)</b>	<b>&lt;0.05</b>	<b>12.9% (27)</b>
<b>CRD**</b>	<b>10.4% (23)</b>	<b>&lt;0.05</b>	<b>6.2% (13)</b>
<b>Stroke</b>	<b>12.2% (27)</b>	<b>&lt;0.05</b>	<b>7.6% (16)</b>
Pulmonary hypertension	12.7% (28)	Ns	12.5% (26)
Varices	8.6% (19)	Ns	5.7% (12)
Rheumatic heart disease	6.8% (15)	Ns	5.7% (12)
Avascular necrosis of bones	25.0% (55)	Ns	25.0% (52)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Mortality	7.2% (16)	Ns	6.7% (14)

\*Sickle cell diseases †Nonsignificant (P>0.05) ‡Red blood cell §Chronic obstructive pulmonary diseases ¶Coronary artery disease

\*\*Chronic renal disease

matory cells, and terminates with endothelial fibrosis and tissue losses in the lungs. Although COPD may mainly be thought of as an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of a disseminated endothelial inflammation all over the body, and close relationships were observed between COPD, CAD, PAD, and stroke (25, 26). For instance, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in smokers, and when the hospitalizations were researched, the most common causes were the cardiovascular diseases again (27). Similarly, 27% of mortalities were due to the cardiovascular causes in the moderate and severe COPD cases in another study (28). Due to the strong atherosclerotic background of COPD and SCDs, COPD may be one of the terminal endpoints of the SCDs (29).

Smoking has major effects on systemic atherosclerotic processes including COPD, digital clubbing, cirrhosis, CRD, PAD, CAD, stroke, and cancers (30). Its atherosclerotic effects are the most obvious in COPD and Buerger's disease. Buerger's disease has never been reported in the absence of smoking in the literature. Smoking induced endothelial damage is probably seen in pulmonary vasculature much more than the other organs due to the higher concentrations of its products, here. But smoking may even cause cirrhosis, CRD, PAD, CAD, stroke, and cancers by the transport of its products within the blood. On the other hand, beside the strong atherosclerotic effects, smoking in human beings and nicotine in animals may be associated with some weight loss (31). There may be an increased energy expenditure during smoking (32), and nicotine may decrease caloric intake in a dose-related manner (33). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (34). Similarly, BMI seems to be the highest in the former and the lowest in the current smokers (35). As a pleasure in life, smoking may also show the weakness of volition to control eating. For example, prevalence of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (36). Eventually, although CAD was detected with a similar prevalence in both sexes, smoking and COPD were higher in males against the higher prevalences of BMI and its terminal consequences including dyslipidemia, HT, and DM in females (30). Probably toxic substances of tobacco smoke cause a diffuse endothelial inflammation all over the body, and it is the major cause of loss of appetite during circulation of these substances within the blood, since the body doesn't want to eat anything during fighting.

Digital clubbing is characterized by increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (37). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (38). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (9). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, and hepatic disorders as those are featuring with chronic tissue hypoxia. As an explanation for that, lungs, heart, and liver are closely related organs and those affect their functions in a short period of time. On the other hand, digital clubbing is also common

in patients with the SCDs and its prevalence was 10.8% in the present study. It may show chronic tissue hypoxia caused by disseminated endothelial inflammation at the capillary level in the SCDs. Beside the effects of SCDs, the higher prevalence of smoking, COPD, and clubbing in males ( $P < 0.001$  for all) may also show some additional roles of smoking, COPD, and male sex on clubbing.

Leg ulcers are seen in 10 to 20% of patients with the SCDs (39), and the ratio was 13.3% in the present study. Its incidence increases with age, male sex, and HbSS genotype (40). Similarly, its ratio was higher in males (19.8% versus 7.0%,  $P < 0.001$ ), and mean age of the patients with leg ulcers was higher than the others (35.3 versus 29.8 years,  $P < 0.000$ ), here. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (39). As evidence of their atherosclerotic natures, the leg ulcers occur in distal areas with less collateral blood flow in the body (39). The hard RBCs induced chronic endothelial damage at the capillary level may be the major cause in the SCDs (40). Prolonged exposure to the hard bodies due to blood pooling in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The hard RBCs induced venous insufficiencies may also accelerate the process by pooling of causative hard bodies in the legs, and vice versa. Pooling of blood in the lower extremities may also have effects on the development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Beside the hard bodies, smoking and alcohol may also have effects on the leg ulcers since both of them are more common in males. Hydroxyurea is the only drug that was approved by the Food and Drug Administration for the treatment of SCDs (12). It is an oral, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (14). Its main action may be suppression of hyperproliferative white blood cells (WBCs) and platelets (PLTs) in the SCDs (41). Although presence of a continuous damage of hard RBCs on endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (42). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to increased WBC and PLT counts induced prolonged endothelial inflammation at the capillary level in the SCDs.

Stroke is also a common complication of the SCDs (43). Similar to acute chest syndrome (ACS) and leg ulcers, it is more common with the HbSS genotype and with a higher WBC count (41, 44). Sickling induced disseminated endothelial damage and activations of WBC and PLTs may terminate with chronic endothelial inflammation, edema, and fibrosis in the brain (41). Stroke may not have a macrovascular origin, instead generalized endothelial inflammation and edema at the capillary level may be much more important in the SCDs. Infections, serious injuries, inflammatory disorders, and other stresses may precipitate the stroke since increased metabolic rate during such events may accelerate sickling and secondary endothelial inflammation and edema even in the brain. Similar to the ACS and leg ulcers, a significant reduction with hydroxyurea may

also suggest that a significant proportion of stroke is secondary to increased WBC and PLT counts induced disseminated endothelial inflammation and edema in the brain in the SCDs (45).

As a conclusion, SCDs are chronic inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Although the relatively younger mean ages, the very high prevalences of hepatomegaly, left lobe hypertrophy, and cirrhosis are probably due to the disseminated endothelial damage, inflammation, and fibrosis both at the arterial and venous systems of the liver, and the left lobe hypertrophy may be a progression step between hepatomegaly and cirrhosis in the SCDs.

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# Histopathological findings in hysterectomy specimens: A retrospective study

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## ABSTRACT

**This is a retrospective study of descriptive patterns of findings seen in hysterectomy specimens based on records from Modern - histopathology laboratory in Aden.**

**A total of 2,544 specimens were analyzed during the 6 year period from January 2006 to December 2012, to study the histopathological findings of these specimens. The age of the patients at hysterectomy ranged from 16-80 years with a mean of 44.6, maximum patients (56.3 %) in the age group 41-50 years and less patients in less than 30 years.**

**Most common pathology findings are, endometrial hyperplasia 1481 (58.3%), non neoplastic cystic lesion 1386 (54.5%), chronic cervicitis 1363 (53.6%), adenomyosis 793 (31.2% ) followed by leiomyoma 697 (27.4%).**

**Other less frequent pathologies identified included atrophic endometrium, inadequate secretory endometrial transformation, gestational trophoblastic disease, endometroid adenocarcinoma, cervical prolapse.**

**This study confirms that benign pathologies are more common in hysterectomy specimens than their malignant counterparts.**

**Key words:** Hysterectomy, endometrial hyperplasia, ovarian cystic lesion, chronic cervicitis.

## Introduction

Uterus, a vital reproductive organ is subjected to many benign and malignant diseases. Many treatment options are available including medical and conservative surgical but hysterectomy still remains the most common gynaecological procedure performed worldwide (1).

The procedure is not well embraced in developing countries, thus, the clinical indications for the procedure should be justifiable, age and parity of the women (2).

In response to the consistent demand for this procedure, hysterectomy has been identified as a key health care indicator in recent reports, to measure and compare hospital performance (3).

It is the definitive cure for many of its indications which include dysfunctional uterine bleeding, fibroids, utero-vaginal prolapse, endometriosis and adenomyosis, pelvic inflammatory disease, pelvic pain, gynaecological cancers and obstetric complications. Ultimate diagnosis is only on histology, so every hysterectomy specimen should be subjected to histopathological examination (4).

In Yemen, histopathological examination of hysterectomy specimens carries diagnostic and therapeutic significance. Prevalence of uterine and adnexal pathologies varies from nation to nation and from region to region (5).

The present study is aimed at detailed histopathological evaluation of all lesions of hysterectomy specimens. It provides an intact uterus and consequent control over tissue sampling and hence enabling determination of origin of particular lesion and to compare the findings with other researchers.

## Material and Methods

Our study was a retrospective descriptive work analysis of 2,544 patients with hysterectomy, over a period of 6 years from January 2006 to December 2012. The information was gathered regarding age, and histological diagnosis and was analyzed by excel program and tables performed according to the objectives of the study and compared to literature review.

## Results

A total of 2,544 hysterectomy specimens between January 2006 to December 2012, were analyzed. The age range of the patients was 16 to 80 years, with a mean of 47.6 years.

Of these 2,544 cases, most of the cases were in the 41-50 years age group 1431(56.3%), which is the most common age group for contracting various diseases as shown in Table 1.

**Table 1: Distribution of patients according to age groups**

Age group (years)	No	%
< 30	50	2.0
31-40	535	21.0
41-50	1431	56.3
51-60	397	15.6
> 60	131	5.1
Total	2544	100

Table 2 reveals that out of the total hysterectomy specimens 1,481(58.3%) were endometrial hyperplasia, atrophied endometrium 396 (15.6%) Tumor was present in specimens out of which 10 was invasive complete hydatidiform mole, 45 were endometrial adenocarcinomas , malignant mixed mullerian tumour (MMMT) 6 (0.2%) cases and one case of choriocarcinoma.

**Table 2: Histopathological findings in Endometrium hysterectomy specimens**

Histopathology	No	%
Endometrial hyperplasia	1481	58.3
Atrophic endometrium	396	15.6
Gestational trophoblastic disease or hydatidiform mole (complete and partial mole)	222	8.7
Inadequate secretory endometrial transformation	216	8.5
Endometrial hyperplasia and Polyp	139	5.5
Endometroid adenocarcinoma	45	1.7
Endometritis	21	0.8
Invasive gestational trophoblastic disease	10	0.4
Atrophic endometrium with polyp	5	0.2
MMMT	6	0.2
Choriocarcinoma	1	0.04
Normal endometrium	2	0.08
Total	2544	100

Most common histopathological abnormality in myometrium was adenomyosis followed by leiomyoma. Adenomyosis in 793 (31.2%), followed by isolated leiomyoma was seen in myometrium of 697 (27.4%) hysterectomies, whereas in 163 (6.3%) myometria, both were present together. Tumor was present in specimens out of which 31 was invasive by malignant endometrial carcinoma as shown in Table 3.

**Table 3: Histopathological findings in myometrium**

Histopathology	No	%
Adenomyosis	793	31.2
Benign leiomyoma	697	27.4
Leiomyoma and adenomyosis	163	6.4
Invasion by malignant endometrial carcinoma	31	1.2
Chronic myometritis	12	0.5
Leiomyosarcoma	10	0.4
Normal	838	32.9
Total	2544	100

In Table 4 (next page) cervix from 2,377 (53.6%) specimens showed chronic cervicitis. Cervical intraepithelial neoplasia (CIN) I, CIN II, CIN III with chronic cervicitis (0.8%, 0.4, 0.3%) and flat condyloma (0.1%, 0.6%), squamous cell carcinoma were seen in 22 specimens (0.9%) and adenocarcinoma were 17 cases. Uterovaginal prolapse were 132 cases (5.2%).

Unremarkable Histopathology of the cervix were 655 cases (25.7%).

2,087 ovarian specimens were retrieved from the computerized database of pathology department, from January 2006 to December 2013. There were 1,386 (54.4%) non-neoplastic functional cysts. The neoplastic were benign serous cystadenoma (2.5 %) and benign ovarian fibroma (0.9%), mucous cystadenoma (0.5%) and mature cystic teratoma (Dermoid cyst) 0.5%. The malignant were 21 cases serous cystadecarcinoma , 9 cases of mucinous cystadecarcinoma , 2 cases were undifferentiated carcinoma and 9 cases of metastatic carcinoma, as appears in Table 5 (next page).

**Table 4: Histopathology of cervix**

<b>Histopathology</b>	<b>No</b>	<b>%</b>
Chronic cervicitis	1363	53.6
Chronic cervicitis with CIN-I	21	0.8
Chronic cervicitis with CIN-II	9	0.4
Chronic cervicitis with CIN-III	8	0.3
Uterovaginal prolapse	132	5.2
Inflammatory endocervical polyp	37	1.5
Flat condyloma without dysplasia	72	2.8
Flat condyloma with CIN-I	4	0.1
Flat condyloma with CIN-II	15	0.6
Flat condyloma with CIN-III	1	0.04
Cervical Leiomyoma	21	0,8
Squamous cell carcinoma	22	0.9
Adenocarcinoma	17	0.7
No cervix	167	6.6
Normal	655	25.7
Total	2544	100

**Table 5: Histopathology of ovaries**

<b>Histopathology</b>	<b>No</b>	<b>%</b>
Non neoplastic cystic lesion	1386	54.5
Ovarian endometriosis	16	0.6
Ovarian fibroma	22	0.9
T.B Oopheritis	3	0.1
Ovarian Bilharziasis	2	0.1
Ovarian abscess	1	0.0
Ovarian hemangioma	1	0.0
Benign serous cystadenoma	63	2.5
Benign mucinous cystadenoma	13	0.5
Mature cystic teratoma ( Dermoid cyst)	12	0.5
Malignant serous cystadeocarcinoma	21	0.8
Malignant mucinous cystadeocarcinoma	9	0.4
Granulosa cell tumor	6	0.2
Sertoli_Leydig cell tumor	3	0.1
Gonadoblastoma	2	0.1
Yolk sac tumor	1	0.04
Clear cell carcinoma	1	0.04
Benign transitional cell (Brunner) tumor	1	0.04
Non Hodgkin's Lymphoma	2	0.1
Undifferentiated carcinoma	2	0.1
Metastatic carcinoma	9	0.4
Normal	511	20.1
No ovaries	457	18
Total	2544	100

## Discussion

Hysterectomy is the commonest gynecological operation and the rate of hysterectomy varies according to geographic distribution, patient and physician related factors (1). Hysterectomy is second only to cesarean section as the most frequently performed major operation in the United States. Approximately 600,000 hysterectomies are performed annually in the USA, and more than one third of US women have had a hysterectomy by the age of (6). In Pakistan, the rate of hysterectomy is quite high because it is the only surgical option available if patient is not responding to medical treatment(7). Many women in Africa and Nigeria in particular are reluctant to undergo this procedure because of the socio-cultural attachment to procreation and taboos associated with lack of menstruation(2). Few studies have been performed describing the pathologic findings in hysterectomy specimen and examining the relationship between the preoperative clinical indication and pathologic diagnosis (8).

In the present study, the mean age of patients was 47.6 years and age range from 16 to 80 years which was nearly similar to findings by others (7,9,10). The peak age for the procedure in our study was the fourth decade (41-50 years) as has been observed in other studies (9).

In the current work we found endometrial hyperplasia was the commonest histopathological finding with 58.3%. Lee (11) reported that endometrial hyperplasia was confirmed in 95%, a somewhat higher figure than we found and less results (16%) were found in Nepal by Ranabhat et al (5). Endometrial hyperplasia is either idiopathic or occurs due to associated diseases or conditions. It can also be transformed to endometrial carcinoma and patients with endometrial hyperplasia must be treated properly and carefully followed up (12). The exact pathogenesis of endometrial polyps is not fully elucidated, but they are thought to originate as a localized hyperplasia of the basalis, perhaps secondary to hormonal influences (13).

In our study the association between endometrial hyperplasia and hyperplastic endometrial polyp were 139 (5.5%) cases. This figure approaches that seen by Kelly et al (14) with (3.1%) in all cases of endometrial hyperplasia in his study period. Other studies have found that incidence of endometrial polyps in endometrial hyperplasia range between 11 and 29% (15).

In the present study we found atrophic changes in 396 cases (15.6%), approximate to that seen by Ranabhat et al (5) with 13% and that seen by Pity et al (16) from Iraq with 10.4 %. A higher figure was seen in a study by Thamilselvi et al (17) with 26%. This may justify by sample size in our study. Other authors were in discordance with our study, Gousia et al (18) reported 5.44%, and the results reported by Sarawathi et al (19) with 2.44%.

In the present study the inadequate secretory transformation were 216 (8.5%) cases, which was similar to other findings (20). It is higher than that seen by Zeeba et al (21) with 1.8% and higher than our result was reported by Sarfraz et al (22) with 24%.

Chronic endometritis is commonly seen in the reproductive age due to either retained products of conception, pelvic inflammatory diseases or other pregnancy related conditions. In our study 21 (0.8%) cases show chronic endometritis of all hysterectomy samples, which approximate the finding of Sajjad et al (23) which was 1% and lower than that seen by Ranabhat et al (5) which was 9.5%. We found in our study endometrial adenocarcinoma were in 45 patients (1.7%). This finding is similar to that found by others (5,16). But it was completely lower than those reported by Patel (24) from Australia 10.5%, and by Gebauer et al (25) from Germany with 16%.

Gestational Trophoblastic Disease (GTD) refers to a wide spectrum of interrelated conditions ranging from benign hydatidiform mole (HM), invasive mole to malignant choriocarcinoma (26). These regional variations have been reported with many speculative factors such as ethnic origin, blood group, age, parity, diet and nutrition, contraception, socio-economic status, immunologic factors and genetic constitution (27). In our study we found 222 (8.7%) cases of GTD of the total hysterectomies samples, only 10 cases were invasive gestational trophoblastic disease at the time of pathological diagnosis and one case of choriocarcinoma.

In the Kingdom of Saudi Arabia (KSA) fifty-nine cases of hydatidiform mole, 36 complete hydatidiform mole (CHM) and 23 partial hydatidiform mole (PHM) and 2 cases of choriocarcinoma were observed, out of 64,762 pregnancies registered at Security Forces Hospital, Riyadh, KSA, during an 11 year period (27). In a study in Nepal, there were 17 (37.8%) cases of hydatidiform mole, 6 (13.3%) of invasive mole and 22 (48.8%) patients of choriocarcinoma (28).

A malignant mixed Mullerian tumour (MMMT) of the uterine corpus is an extremely rare and aggressive malignancy, comprising only 1-2% of uterine neoplasms (29). In our study there was 6 (0.2%) cases of MMT, in the study of Rajshekar only four cases of MMT were diagnosed representing 20% of his sample (30) and this variation in the frequencies may support our justification related to sample size and study design.

In the current study adenomyosis was the commonest lesions of the myometrial pathology and represent 31.1% followed by leiomyoma 27.4%. Adenomyosis appears also to be the commonest pathology and similar to our findings reported by others (5,22,31).

The present study revealed that leiomyoma was also the commonest pathology and it was 27.4%. Reported frequencies vary in different countries and it was 26% in KSA (32), and 36% and in Kurdistan/Iraq (16), in Nigeria 48% (33) and 17% in India (34) and only 8% in Sweden (35). Some of the hysterectomy specimens show more than one lesion in the body of uterus, of which coexistence of adenomyosis and leiomyoma are the most common (34). In the present study there was 6.4% showing coexistence of adenomyosis and leiomyoma. In another study increasing to 56% when adenomyosis with concomitant leiomyoma are included (31) and it was 19% reported by Sarfraz et al (21) and 5.6% reported by Qamar et al (7). Leiomyoma was the commonest lesion of uterine corpus followed

by adenomyosis. This was similar to findings of other studies (16,32,33,36,37). Geographical and racial influences are thus apparent on the prevalence of uterine leiomyoma and the prevalence of risk factors in terms of quantities and type. Early menarche, delayed menopause, decreased parity, obesity and lack of exercise are some of the risk factors of leiomyoma (5).

Among the cervix uteri, chronic cervicitis was the main pathological finding in the present study and accounts for 53.6%. This figure is nearly similar to that reported by Jamal et al (36) which was 41.5% and to that reported by Qamar et al (7) which was 31%. A higher figure of chronic cervicitis seen in Nepal women by Jha et al was 96.4% (37); the variation may be related to different reproductive health procedures. In Yemen almost all males are circumcised which minimizes vaginal infection. In our study 37 (1.5%) cases show dysplasia of various degrees with chronic cervicitis and 20 (0.7%) cases show cervical condyloma with dysplasia.

A premalignant lesion, Cervical Intraepithelial Neoplasia (CIN) was seen in 3.0% in a study by Thamilselvi et al (17) and 0.8 % reported by Ranabhat et al (5). The low incidence of CIN in our study may be related to the reproductive life style, where the women are restricted to single sexual partner, while the CIN is more common with sexually transmitted disease of HPV, which is more frequent in multiple sexual partners women.

The diagnosis of uterovaginal prolapse was based on clinical as well as pathological findings (38). In our study hysterectomies done for utero-vaginal prolapse were found to be 132 (5.2%). This finding was higher than that reported by Pity et al (16) which was 2(0.5%), while less than the findings reported by Butt et al (39) with (11%) and less than 17% reported by Adelusola et al (33). The present study revealed only 0.9% of all the samples of hysterectomy show invasive squamous cell carcinoma at the pathological study. This finding was nearly similar to that reported by Ranabhat et al (5), Gousia RR et al (18) and Bani et al (40) which were 0.6%, 0.3% and 0.6% respectively. This low incidence may be related to reproductive health in Arab and Muslim countries where most of the women are restricted to one sexual partner and a Muslim habit for washing and vaginal douches after sexual intercourse and a high incidence of HPV infection in European countries play an important role in cervical dysplasia and carcinoma.

In the present study adenocarcinoma were 17 (0.7%) cases. Garud et al in 1981 described adenocarcinoma of cervix also carries a considerable percentage, i.e 15-20%, of all invasive carcinoma of cervix (41), while Sanyal et al (42) has noted it as 2% among all cervical lesions. The most common of lesions encountered in the ovary include functional or benign cysts and tumors and benign ovarian neoplasms occur at any age whereas malignant ovarian neoplasms are more common in the elderly (43,10).

Ovarian tumors are one of the major causes of gynaecological problems in females and present marked variation in their histological types. Relative frequency of these lesions is different for Western and Asian countries (10). We found in our

current study, the most common pathological finding of the ovaries in all hysterectomy samples were benign (functional) cysts (54.4%). Our finding was nearly similar to that reported by Mansour (44) in KSA where the benign non neoplastic ovarian cysts comprise 47.5%, while the data from South East Asia shows that 90.5% of ovarian cysts were benign (45); less results were reported by Gupta et al (46) with 2.77% and 20% by Ranabhat et al (5).

Surface epithelial tumours were the major histological type of ovarian tumours followed by germ cell tumours and are the commonest ovarian cyst seen in most of the literature (8). In our study, the most common surface epithelial tumors was benign serous cyst adenoma 2.5% followed by mucinous cystadenoma 0.5%, which approximate the finding seen by Jha et al (37) with 4.5% for benign serous cystadenoma, 3.1% for mucinous cystadenoma and 25.7% of benign surface epithelial tumors were serous cyst adenoma and 6.7 % were mucinous cyst adenoma reported by Pity et al (16) in their study, which was lower than that seen by Abdullah et al (38) where serous cystadenoma represent 44.6% and mucinous cystadenoma 13.6%. The low figure in our study may be related to last study sample, where we select only hysterectomy samples and exclude all cases with simple ovarian cystectomies.

In our study malignant serous cystadenocarcinoma were the most common malignant ovarian neoplasm and represent 0.8% of the cases followed by mucinous cystadenocarcinoma 0.4% and this figure approximates the data published by Jha et al (37) where 3.4% of his cases are malignant serous cystadenoma and 0.8% were malignant mucinous cystadenoma. The higher result with data published by the others, and it's 33.3% for malignant serous cystadenocarcinoma and 15.4% for malignant mucinous cystadenocarcinoma seen by Abdullah et al (38) and in Nepal malignant serous cystadenocarcinoma account 21.1% and 22.2% of malignant mucinous cystadenocarcinoma found by Jha et al (37) and the low figure in our study related to type of study sample. Approximately 95.0% of ovarian germ cell tumors are mature cystic teratomas in the western world (47).

In this study mature cystic teratoma (Dermoid cysts) account for 12 (0.5 %) of all ovarian tumors. A study in Pakistan (48) reported a high figure 38%. A mature cystic teratoma is a benign neoplastic ovarian lesion that occurs during reproductive life and is more common in young females during active reproductive life and usually treated by simple cystectomy and this may justify the low incidence in our study where the hysterectomy is the sample study and not ovarian cystectomy. Other ovarian tumours are rare in our study and it was 0.6% for ovarian fibroma which is similar to that reported by Jha et al (37) with 0.9%. Granulose cell tumor was 6 (0.2%) in our study and it is similar to other findings (37,49).

In the present study ovarian endometriosis accounted 16 (0.6%), which was similar to that seen by Gousia et al (17) with (0.61%). Also, our finding was less than that observed by Randabhat et al (5) which was 8.9% and less than that seen by Ahsan et al (30) with 13%. Ovarian endometriosis is a benign condition usually treated by simple ovariectomies, which justify the low figure in our study which is based on hysterectomy samples.

## Conclusion

Hysterectomy still remains the widely used treatment modality even in developed countries. The ultimate diagnosis is only on histology, so every hysterectomy specimen should be subjected to histopathological examination. Histopathological analysis correlates well with the pre-operative clinical diagnosis for hysterectomy.

Most of the pathologies are still benign; malignancies are also detected on hysterectomy specimens, but very rarely. A yearly audit should be conducted in every institute to collect data and to analyze the pattern of indications and types of histopathological lesions and pattern of diseases.

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# Gastrointestinal Stromal Tumors: challenges in diagnosis and treatment

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## ABSTRACT

**Background:** Gastrointestinal stromal tumors (GIST) are considered the most common mesenchymal neoplasms of the digestive system. They originate from the interstitial cells of Cajal and one of their major characteristics is the over expression of KIT protein Tyrosine Kinase, and they have both diagnostic and therapeutic dilemma. The aim of this study is to present the challenges encountered in the diagnosis and treatment of GIST cases in our facility, Saudi German hospital Riyadh Saudia Arabia during the past 10 years and compare the results obtained with that of other oncology centers. **Patients & Methods:** This study is a retrospective study of cases with GIST that were diagnosed and treated in our center during the past 10 years. These studies include clinical characteristics, target therapy, imaging techniques, histopathology, immunohistochemistry, surgical techniques and prognosis of such cases. **Results:** thirty two patients were diagnosed as having GIST (24 males/8 females) with a mean age 62 years (31-83 years). Diagnosis was made preoperatively in 22 patients (69%)

and intraoperatively with histopathological confirmation in ten patients (31%). The site of the tumor was detected in the stomach in twelve cases (37.5%), two in duodenum (6.25%), ten in small intestine (31.25%), two in mesentery (6.25%), four in colon (12.5%) and two rectal GIST (6.25%). The main presentation of the disease was anemia, GIT bleeding and abdominal mass. Twenty eight patients were considered resectable and they were operated upon (87.5%) and in four patients (12.5%) neoadjuvant therapy was started with favorable response in two cases and poor response in the other two with advanced GIST. All patients received Imatinib as adjuvant therapy. Mean follow up period was 33 months (4-54 months). **Conclusion:** GIST is a challenging malignant tumor that requires a multidisciplinary approach in a highly specialized facility seeking the best management and prognosis.

**Key words:** Gastrointestinal Stromal Tumors; PET; Imatinib; C-KIT Treatment

## Introduction

GIST is defined as a specific, KIT-expressing and KIT-signaling mesenchymal malignant tumor of the GIT [1] that accounts for less than 1% of digestive tract tumors [2]. GIST can develop in the gastrointestinal tract starting up from the esophagus down to the anal canal and it is stated that the stomach constitutes (60%) and the small intestine constitutes (30%) and they are the commonest sites for GIST and the remaining 10% of GISTs are found to be originating from the esophagus, omentum, mesentery, colon or rectum. It is found that up to 30% of GIST show malignant high risk behaviour such as invasion and metastases. [3]. The metastatic behaviour mostly is liver metastases [4]. GIST show over-expression of protein KIT which is a (Tyrosine Kinase) Receptor coded by the c-Kit proto-oncogene on chromosome 4, controlling apoptosis as well as cell proliferation [5]. That protein expression permits the differentiation and diagnosis of those tumors [6]. GIST show almost equal distribution between females and males [7].

In spite of the fact that most GISTs reported cases are sporadic cases there were several patients reported with familial mutations [7].

Diagnosis of GISTs based on histopathological and immunohistochemical studies, also the cornerstone diagnostic test of which is tyrosine kinase receptor KIT (CD117, c kit) expression [8].

Imaging techniques such as CT scan are used for localization of the lesion, and evaluate metastases at the time of diagnosis. Also it is used for evaluation of treatment response and assessment on follow up for detection of recurrence [6]. Endoscopic ultrasound (EUS) is used as an important tool in the GIST diagnosis and is also useful in extracting a tissue biopsy [6]. PET (Positron Emission Tomography) is useful in detecting small metastases which cannot be detected on CECT as it also helps to differentiate between an active lesion from inactive necrotic or scar tissues [9]. Surgery is considered as the standard primary treatment for resectable GIST tumors with no significant morbidity.

Imatinib mesylate (GLIVEC) is an effective and specific approved TKI inhibitor as target therapy for nonresectable or metastatic GIST cases with GIST as an adjuvant and neoadjuvant therapy [10].

Imatinib is very effective in increasing the possibility of negative margin without significant morbidity [11].

## Patients and Methods

This retrospective study was performed on thirty two patients in Saudi German Hospital, Riyadh, Saudi Arabia, from the period from June 2005 to December 2015 reviewing data of the patients, after scientific and ethical approval. Diagnosis included use of upper and lower GIT endoscopy, CT scan, endoscopic ultrasound (EUS), large core needle biopsy (LCNB), fine needle aspiration biopsy (FNAB) and also PET scan. Tu-

mors were evaluated for resectability and complete excision of the neoplasm.

Imatinib mesylate is used for both adjuvant and neoadjuvant patients. Histological parameters were assessed by pathologists for histopathological confirmation of GIST diagnosis and assessment of the immunohistochemical characteristics as well as the mitotic rate and actin, Vimentin and S-100 protein.

The tumors classification was done according to Fletcher's classification matching with guidelines of the American NCI as high, intermediate, low and very low risk [6]. Follow up for the patients was done at 1, 3, and 6 months postoperatively with CT scan then using PET scan every year which was used for evaluation of the occurrence or exclusion of recurrence or metastases.

## Results

32 cases had GIST tumors; 24 male patients and 8 females. 22 cases were diagnosed to have GIST in the preoperative setting by radiological, histopathological and immunohistochemistry examination. 10 cases also had been confirmed postoperatively through histopathological studies held on the surgical specimens; these cases were 2 gastric GISTs, 2 Duodenal GISTs, 2 mesenteric GISTs and 4 intestinal GISTs. Tumor locations were as follows: 12 in stomach, 2 in duodenum, 10 in small intestines, 2 in the mesentery, 4 in the colon and 2 in the rectum.

All patient presentations had variable manifestations such as anemia in 28 cases, gastrointestinal bleeding in

10 cases, abdominal pain in 8 cases, palpable mass in 10 cases, nausea, vomiting in 6 cases, constipation in 4 cases and loss of weight in 12 cases.

Out of the 32 patients in our study 28 underwent surgery and the other 4 non-operable patients at presentation received 400 mg/day glivec as neoadjuvant therapy for 6 months, with convenient response in 2 patients with large GIST detected by PET scan which became operable. On the other hand the other 2 patients had metastases with poor response to the neoadjuvant imatinib therapy and were maintained on the imatinib treatment.

Regarding the surgery type: there were 8 partial gastrectomies, and 4 patients underwent distal gastrectomies and 2 duodenopancreatectomy (Whipple's operation); also 2 excisions of the mesentery with intestinal resection, 10 intestinal resections, 2 transverse colectomies, and 2 anterior resections for GIST of the rectum with all patients having negative resection margins (Table 1 - page 28).

Classification according to Fletcher prognostic scale showed 10 tumors with low risk, 6 tumors at moderate risk and 16 tumors with high risk (Table 2). According to the cell type 20 tumors were fusiform, 8 tumors epithelioid cell and 4 tumors were found to be mixed types. The tumor weight ranged from 205 mg to 12 kg.

**Table 1: Operative procedures performed in 30 GIST Tumors out of 32 Tumors**

Origin of GIST	Type of Resection	No.
stomach	partial gastrectomy	8
	distal gastrectomy	4
mesentry	mesentric excision	2
intestines	intestinal resection	10
colon	transverse colectomy	2
rectum	anterior resection	2

**Table 2: Fletcher Prognostic Classification of 16 GIST Tumors**

RISK	NO.
Very Low	0
Low	10
Medium	6
High	16

**Table 3: Classification of the Patients According to the Immunohistochemistry**

IMMUNOHISTOCHEMISTRY TEST	NO.
Positive CD117,CD 34	28
Positive Vimentin	10
Positive S-100 Protein	8

Immunohistochemistry of 28 neoplasms was + ve for CD 117 and CD 34, 10 patients were + ve for vimentin and actin and 8 patients were + ve for S-100 protein (Table 3). No mortality was encountered in this study but there were 6 morbidities (2 had wound infection, 2 patients with lung affection had medical treatment and 2 patients with incisional hernia had surgical repair done for them.)

Neoadjuvant imatinib was given for 10 patients while adjuvant imatinib was given for 22 patients.

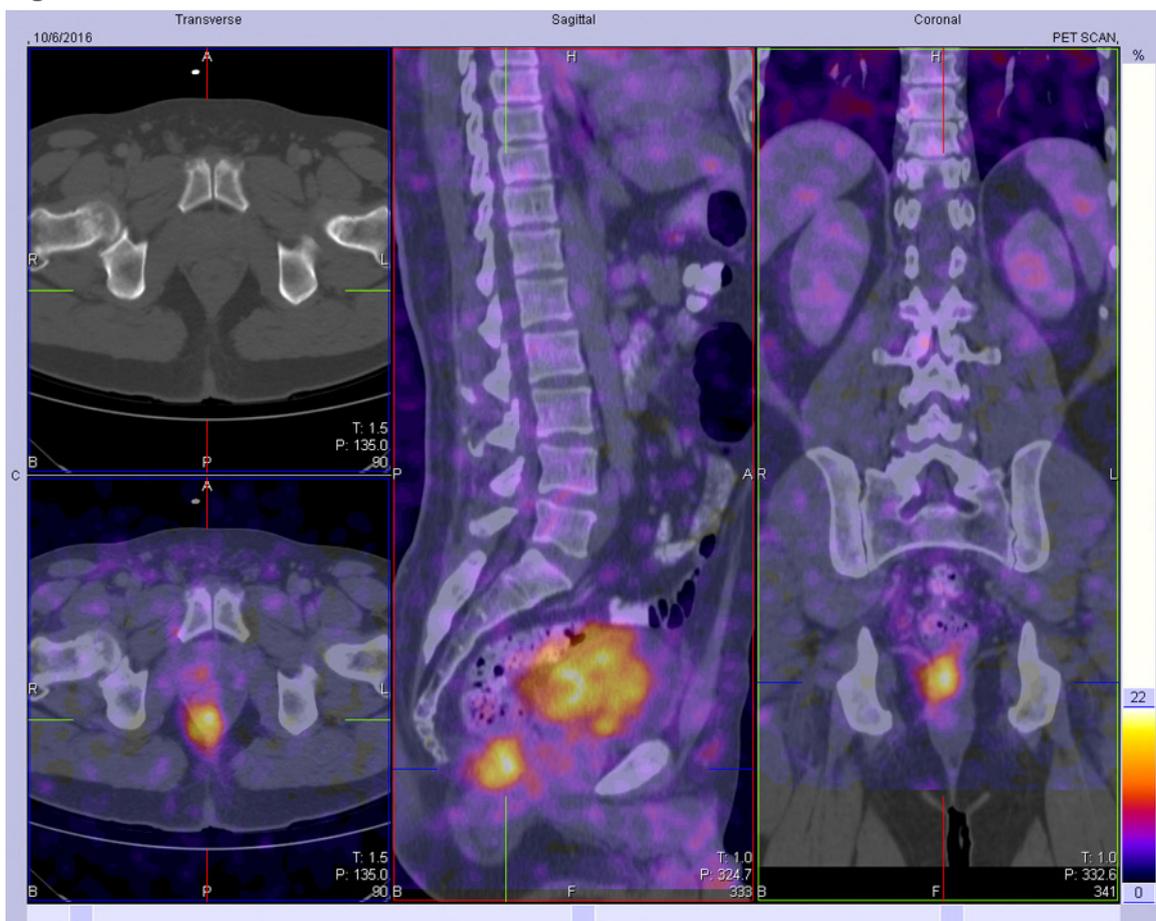
Mean follow up period was 66 months (8-108 months) and during that time 4 patients developed liver metastases. 2 patients who had resection anastomosis for treatment of GIST of the colon presented with liver metastases; also surgical metastasectomy was performed, the other 2 patients had large liver metastases less than one year after surgical resection of intestinal GIST and these 2 patients were put under glivec therapy with poor response, but the course was stationary.

Figures 1, 2 and 3: Active rectal mass

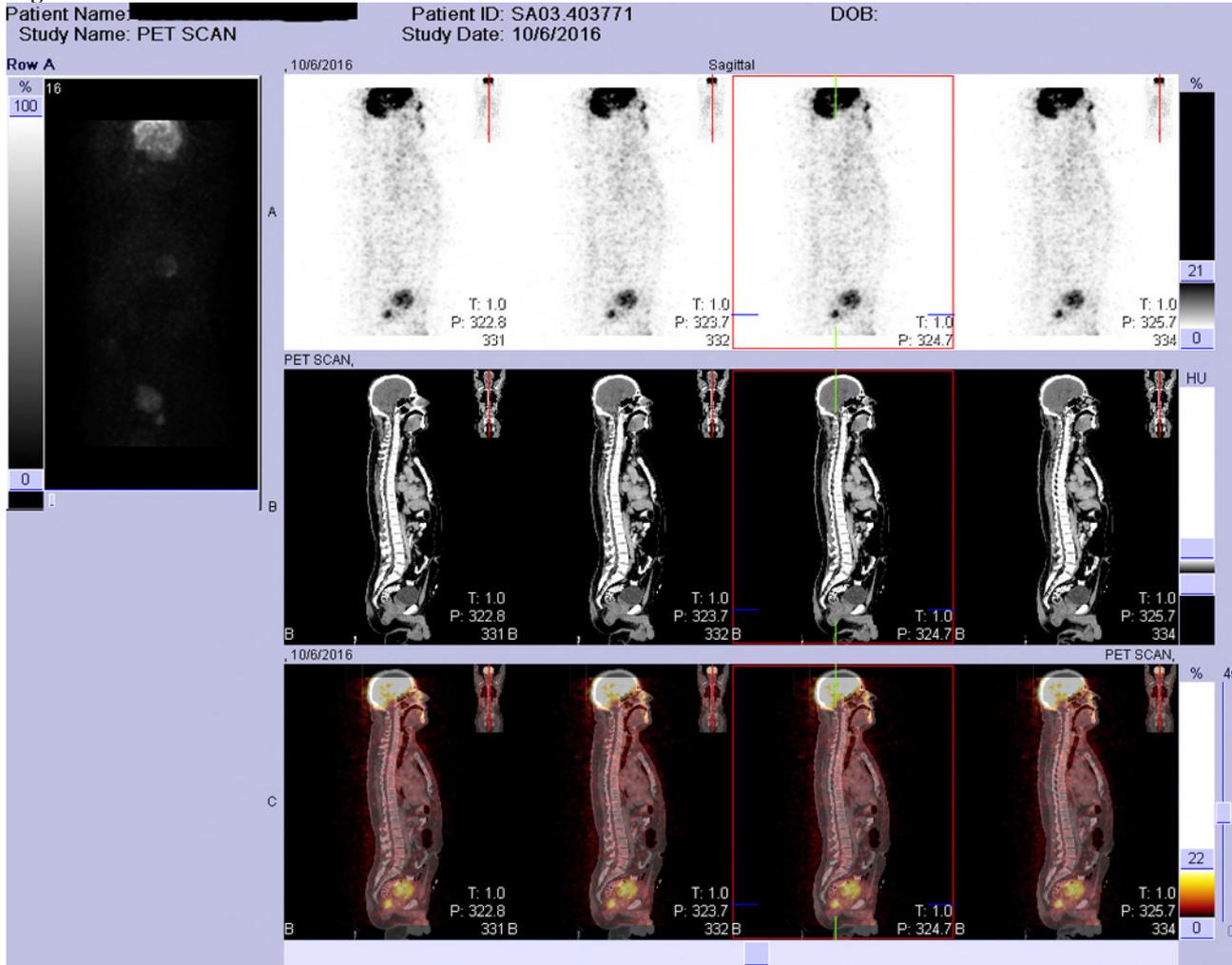
Figure 1



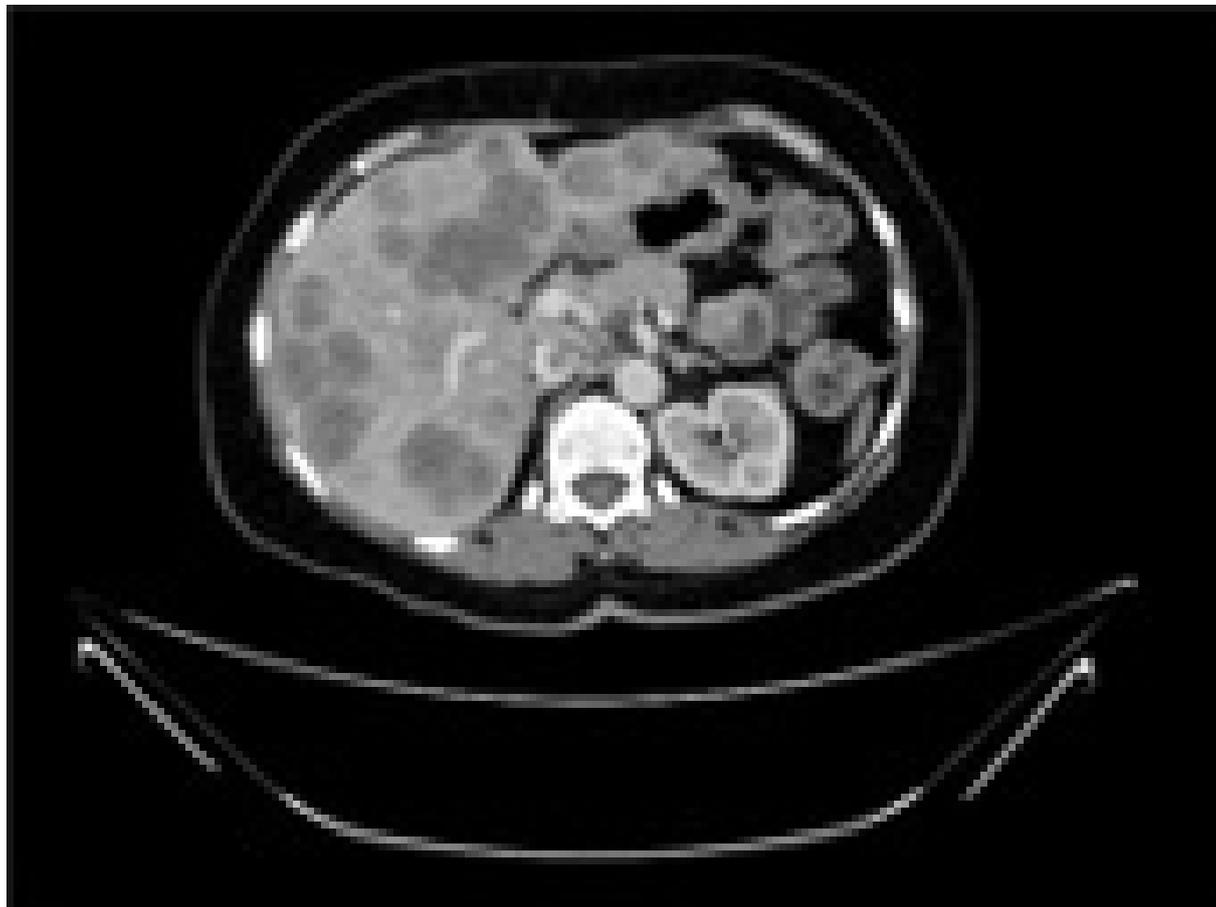
Figure 2



**Figure 3**



**Figure 4: Multiple liver metastasis**



## Discussion

GIST is the most common malignant mesenchymal tumor and originates in the GIT [12]. It is known that these malignant tumors originate from intestinal cells of Cajal [13]. GISTs presented with a variety of clinical manifestations that included abdominal pain, bleeding, intestinal obstruction and (or) perforation [14]. Most common site of GIST is stomach then the small intestine, then colorectal then esophagus followed by the peritoneum, omentum and mesentery [15]. Our study demonstrates a higher incidence in stomach (37.5%) followed by small intestines (31.25%) and then the colon (12.5%) which is matching with what has been stated in the literature.

The most common sign is anaemia [16] and this matches our study as anemia represented 87.5% of the cases.

Bleeding is the most common symptom (30-40%) of cases. The manifestations reported in our study matched those reported in the literature [17].

CT scan is the standard method of choice for diagnosis however Endoscopic biopsy in most cases does not support sufficient proper evidence for establishing GIST diagnosis due to their submucosal nature [18]. This was also encountered in this study as endoscopic biopsy confirmed the diagnosis of GIST in 4 out of 8 cases. [19].

PET-FDG provides information about the tumor activity and showed high sensitivity in evaluating early-and long-term response to glivec in CD 117 positive GIST cases [20].

Choi et al's study showed that CT scan is a specific and sensitive tool to evaluate metastatic GIST response to Imatinib, if response is considered as decreased size more than 15% or tumor decrease more than 20% at 3 months after the start of treatment with a 100% specificity and 97% sensitivity in comparison to the PET response [21]. The consensus of the Lugano conference concluded that PET scan is to be used in cases of early evaluation of response prior to surgical intervention or if metastases are suspected. In our study, only 10 patients had been diagnosed and followed up using PET scan before neoadjuvant Imatinib therapy [22].

As there are multiple differential diagnoses to GIST in GIST histology, this tumor is confirmed through molecular biological and immunohistochemical methods with c-KIT overexpression (CD117) considered the marker of choice. Approximately more than 80% of GIST tumors are c-KIT +ve to CD117, 65-70% are +ve to CD 34, 35-40% +ve to Actin and Vimentin, 4% +ve to S-100 protein and 2% +ve to desmin and or Keratin [23]. In our study 87.5% of cases were found to be positive for CD117 and CD34, 31.25% for Vimentin and actin and 25% positive for S-protein which is matching with other literature. Surgery is the state of the art in the treatment of GIST[24]. In our study, surgery was done for 30 patients (93.75%) with complete surgical excision, while 8 had partial gastrectomy, 4 had distal gastrectomy, 2 had excision of the mesentery with nearby intes-

tine, 10 had intestinal resection, 2 had transverse colectomy, 2 had anterior resection and 2 had pancreaticoduodenectomy for duodenal GIST.

Imatinib Mesylate (glivec) plays a very important role in the management of GISTs and its mechanism is inhibition of c-KIT, which has a major effect in the c-KIT positive GIST[25]. Many studies showed the great consensus that indicates Imatinib mesylate ( glivec ) treatment increases the overall survival in c-kit +ve patients[26].

## Conclusion

Gastro-intestinal stromal tumor (GIST) is considered as a challenging disease in need of a professional multidisciplinary management representing multiple integrated specialties.

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# Progressive Ataxia of Unknown Etiology

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## Introduction

The hereditary ataxias are a heterogeneous group of diseases. Most attempts at classification have been based on pathologic findings and are not always useful for the clinicians. Many of these disorders are multisystem degeneration in which the underlying biochemical or other defect is usually unknown. The pathophysiology is correspondingly poorly understood. Hereditary ataxia can be divided into hereditary congenital ataxia, the ataxia linked with metabolic disorder, and early onset ataxia of unknown etiology (1). (Table 1)

**Table 1: Classification of Hereditary Ataxia**

- |  |
|--|
| <p>I. Congenital Cerebellar Ataxia</p> <p>II. Ataxia associated with metabolic disorders</p> <p>a. Intermittent ataxia syndromes</p> <p>b. Progressive unremitting ataxia syndromes</p> <p>c. Ataxia disorders associated with defective DNA repairs</p> <p>III. Progressive ataxia disorders of unknown etiology.</p> <p>a. Early - onset cerebellar ataxia (onset usually before age 20)</p> <p>b. Late - onset cerebellar ataxia (onset usually after age 20)</p> |
|--|

## Classification

The degenerative cerebellar and spinocerebellar disorders are a complex group of diseases, most of which are genetically determined. Tremendous confusion exists in classifying degenerative disorders causing ataxia, and there is no universally accepted system; these disorders can be divided into two main groups, depending on whether onset of symptoms is before or after the age of 20 years. Most of the early onset are autosomal recessive, and the later onset ones autosomal dominant (2). Most of these disorders are multisystem degenerations in which the underlying biochemical or other defect is usually unknown; the pathophysiology is correspondingly poorly understood. The differential diagnosis of ataxia is important since some of them are treatable if detected early. The discussion will concentrate on progressive ataxia of unknown etiology.

## Progressive Ataxia Disorders of Unknown Etiology

These can be divided into two main groups, depending on whether onset of symptoms is before or after the age of 20 years. Most of the early onset disorders are autosomal recessive, and the later onset ones autosomal dominant (2)

## A. Early Onset Cerebellar Ataxia

### Friedreich's ataxia (FA)

Friedreich's ataxia is the most common of the early onset ataxias. It is one of the best defined and most common forms of hereditary ataxias of unknown etiology(1,2). In some large case series it comprises about 50% of the hereditary ataxia (2,3). It is transmitted in an autosomal recessive manner, with occasional sporadic cases, and usually appearing in childhood or in adolescence but rarely in old age (4). The disease usually progresses slowly without remission, affecting both the central and peripheral nervous system (4,5). The most frequent first symptom is ataxia of gait, although occasionally scoliosis or cardiac symptoms precede definite neurologic symptoms.

The epidemiology of Friedreich's ataxia is perplexing. The clinical features and diagnostic criteria were defined by the Quebec Cooperative Study of Friedreich's Ataxia (QCSFA) (6) and by Harding (1,2) (Table 2). Both authors regarded recessive inheritance, progressive ataxia of limbs and gait and lower limb areflexia as obligatory criteria. The onset, according to the QCSFA and Harding (2, 6), should never occur after the age of 20 years, and always before 25, according to Harding (2). A recent case was reported in the literature where symptoms started at a later stage (7). Both consider extensor plantar response, pes cavus, scoliosis and cardiomyopathy frequent, but not essential signs. Dysarthria, decreased lower limb deep sensation and weakness, obligatory signs for the QCSFA, are not considered essential for an early diagnosis by Harding (2). The diagnosis is made essentially on clinical grounds, CT scan of the brain may show mild cerebellar atrophy.

The prevalence is known only for some populations (3, 8-11). The range is from 0.6 to 1.4/100,000 population. The incidence has been estimated to be approximately 1-2/100,000 (8,12).

In Southern Italy it ranges from 2.1 to 5.4 x 10<sup>-5</sup> (13). Some studies revealed female preponderance (14,15), other series revealed that it occurred equally in males and females (10,16).

Friedreich's ataxia is characterized by degeneration of the spinocerebellar pathways, the dorsolateral columns, and the dentate nuclei (1). There are few changes in the cerebellar cortex itself (1). The cerebrospinal fluid is usually normal and the CT scan of the brain is either normal or shows mild cerebellar atrophy. The primary clinical signs include ataxia, most marked in the lower limbs and often accompanied by dysarthria; nystagmus is usually present in 70% and skeletal-muscle weakness (17). Optic atrophy and retinal pigmentation is usually present. Pes cavus and scoliosis almost always develop (18). Death is usually sudden and may be secondary to cardiac arrhythmias (17). Cardiac involvement is frequent occurring in some 50% to 90% of cases (19); most commonly concentric hypertrophic cardiomyopathy is found (19,20).

A dilated cardiomyopathy has been noted only rarely (21,22), and congestive heart failure is considered a late complication of the disease. There are suggestions that the increase in catecholamine release may contribute to the development of

hypertrophic cardiomyopathy (23). Other authors contest this idea (24).

Multiple studies have shown that the small coronary arteries are abnormal in patients who have cardiac disease and Friedreich's ataxia (25,13). The functional significance of this has been challenged by Hewer (25). Biller et al. (13) reported a prevalence of 1.5% of cerebral infarction in 131 patients. It occurred in half of the patients who developed atrial fibrillation of atrial flutter with underlying symptomatic cardiomyopathy (13). Speech disorder is common in FA (14).

Some dysarthric symptoms include: Sudden pitch changes (this was present in our patient), ataxic staccato, explosive elements, transient harshness, disturbances of respiratory and articulatory control, bradylalia, and dysdiadochokinesia (26,27).

Electrophysiological and pathological studies suggest that axon degeneration and secondary demyelination occur in peripheral sensory nerves (15).

Disease progression is a question open to discussion. It was suggested (28) that axon loss in the peripheral nerve may increase with age. In contrast, some believe (29) that axon loss does not progress during the disease and that further clinical worsening may result from progressive impairment of the cerebellar and corticospinal pathways (29).

Electrophysiological evaluation of FA patients usually includes determination of motor and sensory conduction velocities (MCV, SCV) and multimodal evoked potentials (30). The degeneration of peripheral sensory and somatosensory pathway is usually measured by using nerve conduction studies and somatosensory evoked potential (SEPs) and brain-stem auditory evoked potentials (BAEPs) and the blink reflex (30).

Biochemical alterations observed in this disease include a reduced insulin receptor activity which leads to an insulin resistance state and a reduced glucose tolerance in about 40% of patients (31). Several lipid abnormalities have been noted as well, including a striking reduction in linoleic acid (21), low cholesterol levels with a total cholesterol reduction in serum and in the LDL and HDL fractions are described (21). At the cellular level, deficiencies in activity of the pyruvate dehydrogenase complex and alpha ketoglutarate dehydrogenase complex have been described (32).

The results of therapeutic trials in Friedreich's ataxia with a number of drugs, including choline chloride, lecithine, physostigmine, y-vinyl aminobutyric acid, 5-hydroxytryptophan, benserazide and thyrotropin releasing hormone, have been inconsistent or unconfirmed in terms of producing functional neurologic improvement (2). It was found that the level of the dopamine metabolite, homovanillic acid (HVA) is low in the cerebrospinal fluid (CSF) of patients with either Friedreich's ataxia (FA) or olivopontocerebellar atrophies (31). Amantadine hydrochloride (AH) is known to stimulate dopamine release (34). The use of AH in FA and OPCA was recently tested (35).

**Table 2: Friedreich's Ataxia : Diagnostic Criteria****Essential Criteria for Diagnosis: Present in More than 95% of Cases**

Autosomal recessive inheritance  
 Age at onset of symptoms before 25 years  
 Progressive limb and gait ataxia  
 Absent knee and ankle jerks  
 Extensor plantar responses  
 Motor nerve conduction velocity > 40m/s in upper limbs  
 Small or undetectable sensory action potentials

**Additional Criteria, Not Essential for Diagnosis: Present in More than 65% of Cases**

Dysarthria\*  
 Pyramidal weakness of lower limbs  
 Absent reflexes in upper limbs\*  
 Distal loss of joint position and vibration sense in lower limbs\*  
 Scoliosis  
 Abnormal electrocardiogram

**Other Features Present in 50% of cases or less**

Nystagmus  
 Optic atrophy  
 Deafness  
 Distal weakness and wasting  
 Pes cavus  
 Diabetes

\* Present in nearly all cases within 5-10 years of onset.

Both studies revealed an improvement in reaction time (RT) and movement time (MT). Surgery for foot deformity and scoliosis may be of benefit in well selected patients (36). It is essential to minimize perioperative bed rest. So there is no treatment known to influence the slowly deteriorating disease course. In order to minimize disability and prolong ambulation, strengthening and stretching exercises and functional retraining including aerobic endurance exercise are recommended (36).

**Early - Onset Cerebellar ataxia with Retained Tendon Reflexes**

The other early onset ataxia are listed in (Table 3, next page). They are usually rare, with the exception of early onset cerebellar ataxia with retained reflexes, which occurs at a frequency about one quarter of that of FA, and is often confused with it, but is genetically distinct. The main clinical difference is that the tendon reflexes are normal or brisk in the disorder (23). It is important to distinguish between these two disorders, since the prognosis is better in the former, with patients losing the ability to walk on average 13 years later than in FA. In addition, severe skeletal deformity, heart disease, and diabetes do not occur (24).

**Cerebellar Ataxia with Hypogonadism**

The association of progressive ataxia with hypogonadotropic hypogonadism is rare (2). Neurological symptoms usually develop in the third decade and hypogonadism is obvious at puberty. Neurological syndromes include dysarthria, nystagmus, progressive limb and gait ataxia, mental retardation, dementia deafness, choreoathetosis, retinopathy and sensory loss.

**Cerebellar Ataxia with myoclonus**

The association of cerebellar ataxia and myoclonus, is often referred to as the Ramsay Hunt syndrome. This is a very heterogeneous entity. Some of the identifiable causes include Baltic myoclonus, mitochondrial encephalomyopathy, and sialidosis (24). The rest of cases can be labelled as progressive myoclonic ataxia (24). Symptoms include the development of stimulus - sensitive myoclonus or generalized seizures at the end of the first decade of life. Ataxia and dysarthria develop a few years later with pyramidal signs in the limb. The myoclonic part of this syndrome may respond to clonazepam or valproate sodium with marked improvement in motor function.

Table 3: Early-Onset Ataxic Disorders of Unknown Etiology

Friedreich's ataxia
Early-onset cerebellar ataxia with
Retained tendon reflexes
Hypogonadism
Myoclonus (idiopathic Ramsay Hunt syndrome, progressive myoclonic ataxia)
Pigmentary retinopathy
Optic atrophy + or - mental retardation
Cataract and mental retardation (Marinesco-Sjogren syndrome)
Deafness
Extrapyramidal features
X-linked recessive spinocerebellar ataxia

Table 4: Late-Onset Ataxic Disorders of Unknown Etiology

Autosomal dominant cerebellar ataxia (ADCA) with
Ophthalmoplegia, dementia, optic atrophy, extrapyramidal features and amyotrophy may include Machado- Joseph disease (ADCA type I)
ADCA with pigmentary retinopathy +/- Ophthalmoplegia and extrapyramidal features (ADCA type II)
Pure ADCA of later onset (after age 50) (ADCA type III)
Periodic ADCA
Other syndromes

### Cerebellar Ataxia with Hypogonadism

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## B. Late Onset Cerebellar Ataxia

These disorders have proved the most difficult and controversial in terms of classification (Table 4). The pathological findings are heterogeneous reflecting huge clinical variations in the dominant ataxia (2).

### Autosomal Dominant Cerebellar Ataxia Type I (ADCA Type I).

The age of onset of symptoms in this syndrome ranges from 15 to 65 years but is most commonly in the third or fourth decade of life. Ataxia of gait is the most frequent presenting symptom; it usually involves the limbs and is invariably associated with dysarthria. Early onset usually predicts more progressive disability (37). Associated symptoms may include ophthalmoplegia, nystagmus, lid retraction and optic atrophy. Bulbar symptoms are common during the later stages of disorder and predispose the patient to respiratory infection. Other common symptoms include dementia, extrapyramidal signs, wasting and fasciculation of the face and tongue.

### Autosomal dominant cerebellar ataxia Type II (ADCA Type II).

This is clinically and genetically different from ADCA type I. It is characterized in all families having retinopathy. The age at onset is earlier than that of ADCA type I, most commonly occurring between 15 and 35 (2,38).

### Autosomal Dominant Cerebellar Ataxia Type III

This is a relatively pure cerebellar syndrome in which dementia, ocular or extrapyramidal features do not occur and onset of symptoms are usually after the age of 50 years (39). Nystagmus and pyramidal signs in the limbs are quite common.

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