



PATHO-EPIDEMIOLOGY OF GALLBLADDER LESIONS; A 5-YEAR STUDY AT DOW MEDICAL COLLEGE, KARACHI

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ABSTRACT

Background: Gallbladder and bile duct diseases are relatively common, with cholelithiasis on the top of the list, affecting 10–15 % of the world population. A wide variety of these diseases are seen as a reason for admission to surgical wards.

Objective: The intention of this study is to audit the range of the histopathological spectrum detected in gallbladder specimens from a tertiary care hospital of Karachi and, particularly, to determine the prevalence of incidental gallbladder malignancy in our population.

Methods: This retrospective, descriptive, cross-sectional study design used recorded data of all the gall bladder histopathological samples received in the Department of Pathology. We used the data obtained over a period of five years - 1st January 2014 to 31st December 2018 - to update the trend of gallbladder pathologies in our local population.

Results: Amongst the 948 specimens included in the study, mean age was 39.01 years (range 10-89 years), 834 (87.8%) were females and 114 (12.0%) were males. Regarding the reason for the presentation, the most common presenting complaint reported was Right hypochondrial pain 752 (79.3%), followed by epigastric pain 307 (32.4%), vomiting 242 (25.50%), and nausea 190 (20.0%). Cholecystitis was the most commonly encountered diagnostic entity 944 (99.58%) ; with the chronic variety being the most frequently found , followed by cholelithiasis 642 (67.72%), cholesterolosis 30 (3.16%), follicular cholecystitis 9 (0.95%), adenocarcinoma 4 (0.42%) and xanthogranulomatous cholecystitis 3 (0.32%)

Conclusion: There is no concept of social security and health insurance among the masses, largely in part due to lack of awareness, lack of education, and lack of funds to buy insurance in the first place. As a result of a lack of screening programs in our country, Gall bladder lesions and carcinoma is fairly underreported. We suggest the development of nation-wide screening programs.

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INTRODUCTION

Gallbladder and bile duct diseases are relatively common, with cholelithiasis on the top of the list, affecting 10–15 % of the world population. A wide variety of these diseases are seen as a reason for admission to surgical wards. The underlying pathogenesis is variable, such as factors predisposing to stone formation; either cholesterol or pigment stones; i.e. changes in bile composition, gallbladder hypomotility(1), ductal obstruction, infections, etc. Paediatric manifestations of gallbladder inflammation are frequently seen as acute acalculous cholecystitis, accounting for around 50% to 70% of cases of acute cholecystitis in children(2). Common symptoms representing underlying gallbladder complaints usually range from pain in the abdomen, nausea and vomiting, to fever and jaundice. Many patients visiting the medicine subspecialty are also frequently referred to the surgical department with regards to these complaints.

Studies claim that about 40% of investigations carried out in the absence of gross abnormalities are unnecessary. It is not only expensive but is also putting a burden on histopathology department(3). In Pakistan the average expense and time spent on processing one specimen is approximately 20-40 USD (1 USD=163.74 PKR as of Oct' 2020) and 50-60 minutes respectively(4). In lieu of all the available data, we have concluded that despite extensive research on the underlying factors, susceptible candidates, risk factors, etc; there remains a paucity in the data at a regional level, especially with regards to the array of gallbladder and related diseases among the local i.e. Karachiite(Pakistani) population.

The intention of this study is to audit the range of the histopathological spectrum detected in gallbladder specimens from a tertiary care hospital of Karachi and, particularly, to determine the prevalence of incidental gallbladder malignancy in our population. This would pave the way to charting

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recommendations for future practice and the necessity of routine histological examination of gallbladder specimens in a developing country like Pakistan.

METHODS

This retrospective, descriptive, cross-sectional study design used recorded data of all the gall bladder histopathological samples received in the Department of Pathology. We used the data obtained over a period of five years - 1st January 2014 to 31st December 2018 - to update the trend of gallbladder pathologies in our local population, analyze the prevalence of specific gall bladder pathologies in particular age groups and report the gross and microscopic findings mentioned in the histopathological reports of the specimens to classify various benign and malignant presentation of gallbladder diseases.

Consolidated data included all the gall bladder specimens acquired during the aforementioned time period under study, irrespective of the individual diagnoses. We encountered a total of 949 samples obtained through the surgical procedures of open cholecystectomy and laparoscopic cholecystectomy. There was no age limit in our data collection and we considered both male and female genders.

The materials that we used included patient case files, histology request forms, and histopathology reports. However, the data utilized was archived with the original materials consisting of slides of biopsies and tissue blocks preserved in 10% neutral buffered formalin. The specimen underwent both gross and microscopic examination by histopathologists and were diagnosed as cholecystitis, xanthogranulomatous cholecystitis, follicular cholecystitis, cholelithiasis, cholesterolosis, and adenocarcinoma.

Proforma

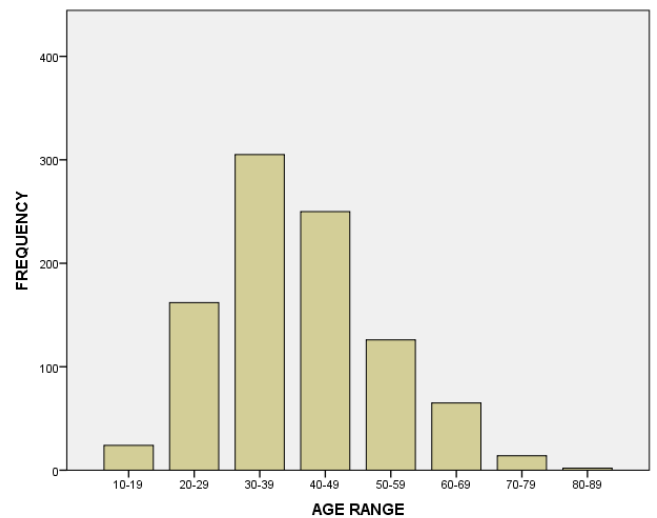
We set forth a proforma delineating imperative details including histopathological number, name, age, hospital ward, nature of the specimen, clinical presentation, surgical procedure, and diagnosis. We broadly categorized the diseases into cancerous and non-cancerous, with non-cancerous including cholecystitis, xanthogranulomatous cholecystitis, follicular cholecystitis, cholelithiasis, cholesterolosis and adenocarcinoma in the cancerous lesions.

Statistical Analysis

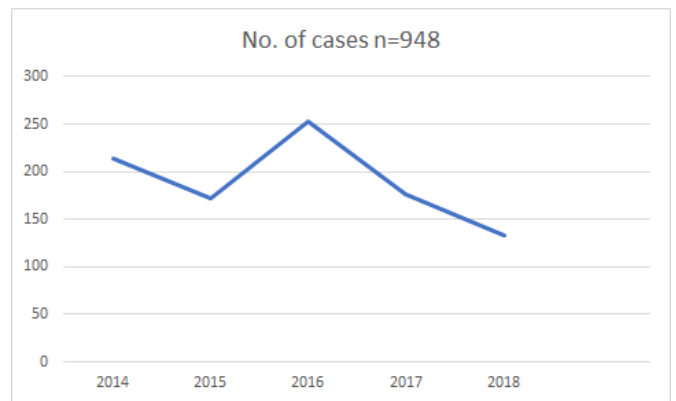
All the data was entered and analyzed on IBM-SPSS version 24.0. Means ± standard deviations were computed for continuous variables and frequency distributions and percentages were calculated for categorical variables. Bivariate correlations were computed for significant observations using Pearson’s correlation coefficient.

RESULTS

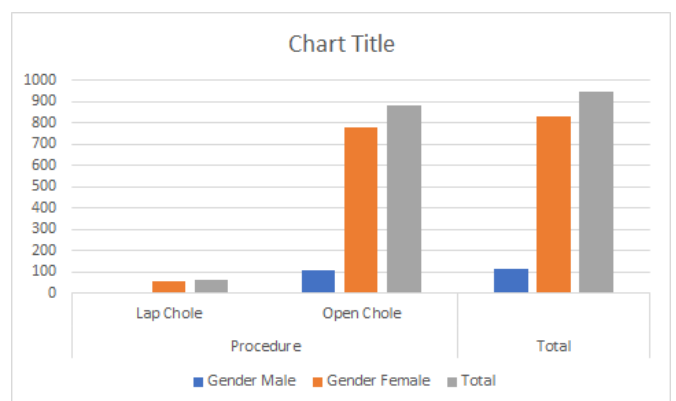
During our study period of five years, 948 specimens were collected at the Pathology Department, Dow Medical College (DMC). Mean age of the patients was 39.01 years (range 10-89 years) and most of the patients were 30-39 years of age (Figure 1).



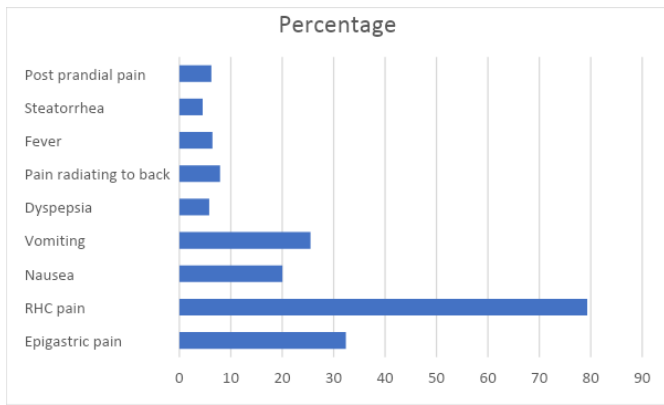
Out of the total cases, 834 (87.8%) were females and 114 (12.0%) were males. The yearly frequencies of the cases received from 2014-2018 are shown in Figure 2, with the highest number of cases in 2016 (n=253, 26.7%).



Two procedures were carried out, namely Laparoscopic cholecystectomy and open cholecystectomy (Figure 3), with the latter being the more common procedure (93.5%).



Regarding the reason for the presentation, the most common presenting complaint reported was Right hypochondrial pain 752 (79.3%), followed by epigastric pain 307 (32.4%), vomiting 242 (25.50%), and nausea 190 (20.0%), with the others being represented in a smaller percentage of people as shown in Figure 4.



Cholecystitis was the most commonly encountered diagnostic entity 944 (99.58%); with the chronic variety being the most frequently found, followed by cholelithiasis 642 (67.72%), cholesterolosis 30 (3.16%), follicular cholecystitis 9 (0.95%), adenocarcinoma 4 (0.42%) and xanthogranulomatous cholecystitis 3 (0.32%) as shown by Table 1.

Table 1 Age and sex distribution of Histological Diagnoses.

Histological Diagnosis	n (%)	Male n=114 (%)	Female n=834 (%)	Mean age (years) ± SD
Cholecystitis	944 (99.58)	113 (99.12)	831 (99.64)	38.97 ± 11.995
Xanthogranulomatous Cholecystitis	3 (0.32)	1 (0.87)	2 (0.24)	48.33 ± 6.506
Follicular Cholecystitis	9 (0.95)	0 (0)	9 (1.08)	46.78 ± 16.239
Cholelithiasis	642 (67.72)	79 (69.29)	563 (67.51)	38.84 ± 11.877
Cholesterolosis	30 (3.16)	3 (2.63)	27 (3.24)	36.50 ± 9.519
Adenocarcinoma	4 (0.42)	1 (0.87)	3 (0.36)	58.00 ± 11.662

Table 2 Correlation of cholecystitis with chorionicity, wall thickness and number of stones

Chorionicity	Wall thickness		No. of stones		
	Thick	Thin	Single	Multiple	None
Acute	5	5	0	4	1
Chronic	848	546	155	620	67
Acute on chronic	51	37	13	34	7

DISCUSSION

In our study, a record of histopathological specimens over a 5-year time span from 1st January 2014 to 31st December 2018 was used. The mean age of the participants was 39.01 years and most of the participants belonged to the age group of 30-39 years. This is in line with the findings of previous studies that show the occurrence of gallbladder diseases in the age range of 26-35 years in both genders and is also consistent with the findings in other Asian countries including a study conducted in Pakistan(5). However, this contradicts findings from Western studies that show a higher prevalence of gallbladder disease in the elderly population(6).

In our analysis, we scrutinize the correlation of some histological variants of gallbladder lesions with some clinical criteria such as age and presenting complaints of the patients. Both cholecystitis and cholelithiasis were seen most commonly in the 30-39 years age group, whereas adenocarcinoma was seen in the 50-59 years age group. Our population tends to consume meals rich in saturated fats and consume fewer vegetables. Additionally, there is a widespread

use of cocaine and smoking. A possible reason for the later presentation in Western studies could be due to that individuals in this age group tend to be more sedentary and thus obese, thereby predisposing to gallbladder conditions.

We had a total of 948 specimens received over our 5-year study period from 2014 to 2018. Despite the fact that this is a well-researched topic, some gaps in academia have been noticed and this study helps identify and fill them to a certain extent. Of course, future studies on a much larger scale are needed in order to get a birds-eye view on the ever-evolving problem of gallbladder diseases. Our study helps identify this cohort of pathologies in a predominantly rural population presenting to a government-run tertiary care hospital in a lower-middle-income country (LMIC). Recent studies targeting a similar aspect of research that has been performed in our region, at a private hospital primarily catering to affording and hence 'urban' population, or have been performed in other cities of Pakistan(6, 7).

Unlike the developed world, there is no concept of social security and health insurance among the masses, largely in part due to lack of awareness, lack of education, and lack of funds to buy insurance in the first place. The trend of histological examinations was seen to undergo a significant decline from 2014 (22.6%) to 2018 (14.0%) but the greatest influx was seen in 2016 with a total of 253 cases. One reason for the overall declining trend could be probably owing to better clinical diagnosis and clinical screening at grass-root levels thereby reducing the need for and the burden of biopsy. The most commonly identified lesion in our series was cholecystitis (n=944) followed closely by cholelithiasis (n=642), whereas adenocarcinoma was only seen in 4 cases overall.

The main strength of this study is the standardized review of pathological materials for each specimen received. This yielded 944 cases of benign diagnoses and 4 cases of adenocarcinoma out of the total 948 cases that were studied. The gallbladder samples in our series were mainly collected via two procedures; namely open (886 specimens) and laparoscopic cholecystectomy (61 specimens). However, laparoscopic cholecystectomy is considered the gold standard for the management of gallbladder disease(8), open cholecystectomy was the more commonly performed procedure.

Usually, open and laparoscopic modalities are compared and discussed in literature and not many report a comparison of outcome for surgical versus medical management(9), including ours. As such, we feel the need for more research in this domain. Considering the undue healthcare burden all these services and surgeries are; many say that only the most suspicious or those with gross abnormalities should be submitted for histopathological analysis(10).

A majority of our sample population was female (87.8%) as seen in numerous previous studies highlighting the prevalence of gallbladder diseases in females(6). The South Asian society is built up in a way to make it difficult for females to leave the house as per their needs. This, therefore, emphasizes the need for outreach screening programs in remote and poorer areas, where non-affording, logistically challenged individuals can be approached and helped.

Our results are limited to cases within our regional confines, hence they are not representative of a global population of gallbladder cases. It is, however, important to note and take

into account the fact that Karachi is one of the largest and most densely populated cities of Pakistan and is also the main Metropolitan center known and easily accessible to the residents of Interior Sindh, Baluchistan and even regions as far as Afghanistan and Iran. Another important consideration regarding this is that patients presenting to us, usually do so at the last moment. They are not well-educated if not illiterate, especially regarding their own health conditions. There is a significantly low follow-up attendance as well, either because of lack of funds to afford health services, or else as in our situation; where despite being a government hospital and most of the amenities being free of cost, transportation issues are present whereby they are either non-accessible or can't be afforded.

Late presentation not only translates into acute discomfort but also into chronicity of the condition. A previous study found that the chronicity of gallbladder disease was significantly correlated to the presence of adenocarcinoma(8). In our study, we found that 0.4% of our 948 cases were of adenocarcinoma.

Geographic variations have also been noticed. Countries in South America including Bolivia and Chile have reported a high incidence. Korea, Japan, and China in Asia and the central European region including Poland, the Czech Republic, and the adjoining countries are areas with a moderate incidence of gallbladder cancer(11). Likewise, it has also been reported that the neighboring countries in the Indian subcontinent like India, Nepal, and Bhutan also have a high prevalence of GBC(8). A low incidence of GBC has been reported in Sri Lanka, the Maldives, Yemen, Afghanistan, and Turkmenistan(8).

The findings of our study are in line with another study in Pakistan conducted by Shafique *et al.*(7) that reported a frequency of 0.7%. However, other Pakistani studies show a slightly higher frequency of adenocarcinoma of around 2.7% among patients with gallstones(10), and it has been found to be about 8% in Karachi specifically(12).

The Globocan 2018(13) data showed that gallbladder cancer accounts for 1.2% of all global cancers diagnosed, and about 1.7% of cancer-related deaths. Despite the fact that gallbladder cancer is a rare disease, it has a poor prognosis and more often than not, is aggressive in nature. It is important to notice in previous studies that if screened and discovered earlier and hence treated earlier; 75% of patients have been found to survive for up to 5 years(6).

It has long been postulated that gallstones increase the risk of the subsequent development of gallbladder cancer(14). Long-standing gallstone disease (GSD) as well as the large size of the stones themselves serve as risk factors for the development of gallbladder carcinoma(8), with the risk going up about 4 to 7 times from baseline(14, 15). Other risk factors include polyps > 1 cm, anomalous junction of the pancreaticobiliary junction (AJPBJ), chronic bacterial infections, typhoid carrier state, familial and genetic factors, occupational and environmental toxins and carcinogens, hormonal changes in females(16), and some social factors as well as high parity, low fiber and vitamin intake, high fat intake, long durations of fasts, and using repeatedly boiled or improperly stored ghee(12). It is of note that gallstones can become colonized by bacteria over time thereby triggering an inflammatory process, causing the release of cystic enzymes from bacteria which

cause hydrolysis of conjugated bilirubin as well as fatty acids(6).

A study reported that rural residence is associated with an increased risk for GBC(8). Kumar *et al.*(17) reported that 54% of patients with GSD resided in rural areas, as well as 80% of those with GBC.

Infection with salmonella typhi once established, is difficult to completely treat with antibiotic treatment, especially in the presence of cholelithiasis(18). This is partly because the stone offers a surface for the formation of bacterial biofilms thereby facilitating the prosperity of the bacteria(18).

This highlights the importance of early screening and effective detection of gallbladder lesions since they can ultimately progress to carcinoma. This will help to stop the progression at an early stage and dramatically improve prognosis. The aggressive nature of the tumor makes for rapid spread to the adjacent anatomical areas(8). This pattern of spread deems the tumor unresectable at presentation, further adding to the already poor prognosis(8).

The overall prevalence of gallstone disease has been found to be 22% in Uganda(19). There are many risk factors for the development of gallstones specifically in Asian countries, including female gender, fertility, middle age, etc(19). Certain comorbidities have also been identified including Crohn's disease, ileal resection, and other diseases of the ileum, etc(6). There are socioeconomic and environmental factors that include advancing age, low socioeconomic status, poor sanitation, environmental pollutants, heavy metals, as well as smoking and tobacco chewing(8). Aune d's meta-analysis(20) found a dose-response relationship between smoking and GBC, while an Indian study showed that a similar increased risk for GBC was associated with chewing tobacco(21).

Due to the general poor sanitation and lack of basic hygiene, there is a strong association between causative infections like chronic Salmonella typhi (*S. typhi*) infection, Helicobacter pylori (*H. pylori*) infection(8, 18). It has been found that chronic salmonella carrier status predisposes to carcinogenesis(8).

In our series, we used the patient data to identify the presenting complaints. The most common presenting complaint in our series was right hypochondriac (RHC) pain, with a frequency of 79.32%. This is similar to the findings of a North Indian study however they reported a higher frequency of 98% (8). A study conducted in Pakistan by Siddiqui *et al.*(10), also reported RHC pain as the most common presentation, albeit with a higher frequency of 91.4%.

Pakistan is an agricultural country, and as such agricultural runoff into rivers is fairly common. These rivers are directly used by the people living around it and also generally by means of nation-wide water supply; and are consumed by people. Not only this, but water contamination by industrial waste and human sewage dumping into the water supply have been identified as important risk factors(8). It is thus important to notify the respected authorities regarding the proper disposal of factory effluents, etc.

There are many underlying reasons for the female predominance of gallbladder diseases.

Literature shows that female hormones like estrogen predispose to gallstone formation by increasing the biliary cholesterol saturation index. Estrogen and progesterone are also responsible for the predominance of cholecystitis in females(6). Estrogen and progesterone receptors are present on the gallbladder mucosa and may promote stasis and thus cholelithiasis(8). Since these predispose to infection, it allows for greater exposure to bacterial and chemical toxins.

These hormones increase during pregnancies(8). This is of great social importance, since in Pakistan and the neighboring South Asian countries like India, Nepal; women are younger at the time of their marriage(8). With a younger age at first pregnancy and a greater number of overall gestations than their Western counterparts; there is a greater overall prevalence of gallbladder disease in the younger population in these countries.

As such, the most common histopathologic diagnosis in our series was that of cholecystitis, closely followed by cholelithiasis (67.732% overall). This is in line with findings from other studies. Our study reports a prevalence of 99.64% of cholecystitis cases in females alone, with the chronic variety being the most common subtype (89.72%). We also found that chronic cholecystitis was mostly associated with multiple gallstones. One interesting risk factor for cholecystitis is iron deficiency anemia(22), and as it is fairly common among females in Pakistan; As such, adequate iron supplementation should be provided to women, especially those of childbearing age owing to a loss in menstrual blood as well as low iron intake in food. Other factors that have been found to contribute to the higher prevalence of cholecystitis among females include multiparity(8), high Body mass index (BMI), oral contraceptive use, and hormone replacement therapy. An Indian study found that of the cases of GBC, 87% used oral contraception(23).

We identified only 3 cases (0.32%) of xanthogranulomatous cholecystitis in our series, and these were found to occur at the mean age of 36.50 years. These findings are similar to those of a recent Pakistani study; which reported only 2 cases of XGC aged 35 and 40 years respectively(7). However, these are contradictory to the findings of a study that reported XGC commonly occurs in individuals below 30 years, whilst Singh *et al* reported the occurrence of XGC in the 6th and 7th decade of life(24).

Of the samples, we found a total of 31 (3.9%) cases of cholesterolosis. This is contrary to a study conducted in India that reported 6% of their cases to be cholesterolosis(25), whereas another Indian study reported a frequency of 2.9%(24). Cholesterolosis is associated with mucosal villous hyperplasia, together with the accumulation of cholesterol esters within the macrophages. They often tend to be asymptomatic, and cannot be efficiently diagnosed by ultrasonography(26).

About 0.95% of our cases were of follicular cholecystitis (FC) which, as previously mentioned, was the only entity in our series to be more common in men as compared to women. This is lower than values reported by an Indian study which showed a frequency of 5%(25). First described in patients infected with Salmonella in the early 1900s. A characteristic histologic finding is a dense inflammation forming follicles. The inflammation is follicular in nature, with a predominance of lymphocytes; which are also normally found in the gallbladder

mucosa. Oftentimes, chronic changes such as Rokitsansky-Aschoff sinuses and fibrosis can also be found in the underlying tissue(27).

Since most cases show mottled FC, there is a high chance that these lesions go undiagnosed. Our study found that of the 4 total cases of adenocarcinoma in our series, 3 were in females and the other one was in a male patient. Jain *et al* reported that the observed risk is higher among women as compared to men, (OR 6.04; 95% CI: 4.52–8.07 versus OR 3.17; 95% CI: 2.23–4.50) (28). It is important that patients presenting with symptomatic cholelithiasis should be treated and that every cholecystectomy specimen should be subjected to thorough macroscopic as well as histopathological examination to conform any diagnosis that might otherwise be missed out. It is a notable finding that chronic gallstone disease paves way for subsequent adenocarcinoma; and since the former is more common in females it is fair to say that the latter will follow suit. Early cholecystectomy should be offered to patients with symptomatic gallstones who are at high risk of carcinoma(8). Of all the risk factors associated with GBC, GSD is the most readily identifiable and thus can be targeted to prevent subsequent GBC.

As a result of a lack of screening programs in our country, incidental GBC is fairly underreported. We suggest the development of nation-wide screening programs such as those inundated in Latin American countries like Bolivia and Chile(8). These screening programs would detect GSD in women >40 years and men > 50 years. This is an expectant policy and other countries like Western Europe and Northern America report lower levels of progression to GBC due to the efficiency of these screening programs. The masses should be educated about symptoms and what they could possibly mean, and should be discouraged from alternative therapies and household remedies, and should be advised to seek medical attention at the earliest.

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