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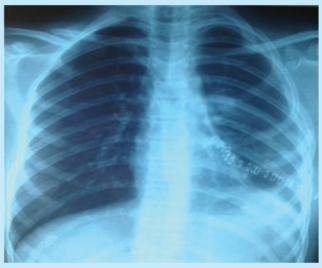
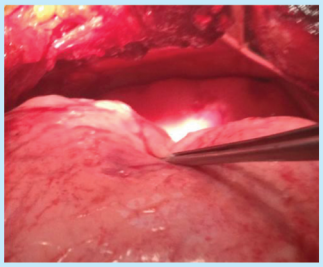
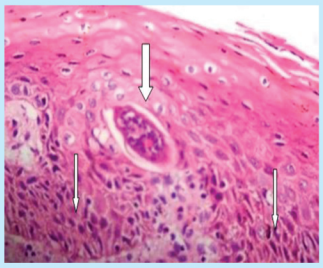

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JOURNAL CONTACT

Yemeni Journal for Medical Sciences P.O. Box: 13064 Tel.: 00967 1 373237 Ex. 4209

PRINCIPAL CONTACT

Mohammed Mahdy
Associate Professor
Yemeni Journal for Medical Sciences
Phone: 00967 1 373237 Ex. 4209
Email: yjms@ust.edu

SUPPORT CONTACT

Hudhaifa Hasan
Phone: 00967 1 373237 Ex. 4209
Email: ustj@ust.edu

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YEMENI JOURNAL FOR MEDICAL SCIENCES

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ORIGINAL ARTICLE

Perception of Radiologists about Diagnostic Errors in Radiology in Yemen

Aklan H.M.[1,*]

[1] *Department of Radiology, Faculty of Medicine and Health Sciences, University of Science and Technology, Sana'a, Yemen*

[*] **Correspondence author:**
E-mail: h.aklan@ust.edu

Abstract:

Background: Errors of diagnosis in Radiology are common, which affect patient's care and management. Several types of radiological errors such as misperception, miscommunication, and procedure misconduct have been reported highlighting the importance of Radiologists' awareness about their own errors. However, no data are available from Yemen. The aim of this study is to assess radiological errors in Yemen.

Method: A standard questionnaire of radiological errors was distributed conveniently to radiologists in the main public and private hospitals in Sana'a city, Yemen.

Results: Of 80 questionnaires distributed, 58 were returned back (the response rate was 72.5%). About 88% participants had diagnostic errors in 2013. The radiology errors were classified as under-call (false negative) (29.3%), communication errors (27.6%), overcall (false positive) (25.9%), procedural complication (24.1%) and interpretation errors (15.5%). Lack of previous studies and inadequate clinical information were mentioned as causes' errors (37.9% and 36.2%, respectively). Most radiologists (70.7%) did not keep record for their own errors, and only 24.1% of radiologists had errors meeting in their departments.

Conclusion: It has been concluded that errors in radiology are still a significant problem affecting patient safety. Collaborative efforts must be established to reduce diagnostic errors in radiology through organizing regular meetings to educate radiologists about such matter and create a good environment for learning and improvement rather than blaming and embarrassing.

Key words: Errors, Radiology, Yemen

1. Introduction

Diagnostic errors in radiology are common leading to an ultimate effect on patient care and management (1-3). It was estimated that the incidence of plain radiographs errors is 10-20% and it is higher in cross-sectional imaging (4). Radiological errors can be classified into errors due to misperception, miscommunication, and procedure misconduct (5). Health care providers are recommended to implement an effective system for detecting and preventing the radiology-related errors (1, 3, 6, 7).

Good reporting of radiological errors will improve the quality care and patient safety (4, 8). Regular meeting to discuss radiological errors is a significant tool to minimize the occurrence of the diagnostic errors in radiology, which should be conducted in the radiology department. In the meeting, radiologist will be exposed to errors made by their colleagues and will get more experience and enhance his practice (2, 4, 6, 9). Identifying and reducing the radiological errors will decrease the mortality, morbidity, and the cost of the healthcare services as well as the duration of the stay in the hospital (10).

Few studies were done to assess radiologists' perception about their own errors and how they deal with them (4, 9). However, no study has been conducted in Yemen. Thus, this study aimed to evaluate radiologists' perception about their own errors and to assess the existing system to record and report radiological errors in Yemen. The study may reduce the radiological diagnostic errors, improving the patient care and decreasing the healthcare cost.

2. Methods

Subjects

A cross-sectional study was conducted in seven public and private hospitals in Sana'a city, including UST Hospital, Saudi German Hospital, Althawrah Hospital, IbnSina Hospital, Sab'een Hospital, Police Hospital and Alkuwait Hospital. All radiology technicians, residents and consultants working in the hospitals were invited to participate based on voluntary bases. Informed consent was obtained from each one who agreed to participate after clear explanation of study's objectives. Study's protocol was approved by the ethical committee of faculty of medicine, university of science and technology, Yemen.

Questionnaire

A standard questionnaire of errors in radiology was disseminated conveniently to radiologists, consultants, residents, and technicians in Sana'a city, Yemen. The questionnaire contained participants' demographic characteristics, participants' perception of radiological diagnostic errors. It evaluates the frequency of errors, their causes and classification, experience of recording system and error meetings. Participants were interviewed by well-trained interviewers.

Statistical analysis

Data analysis was performed using Statistical package for Social Sciences (SPSS) software version 20. Frequencies of errors were calculated and data were presented in tables.

3. Results

Of 80 persons invited to participate, 58 were agreed to join the study (the response rate was 72.5%). Of them, 40 individuals were males (69%) and 18 were females (31%). The majority of participants were radiology technicians (53.4%),

followed by radiology consultants (37.9%). Most of the participants are working in the University of Science and Technology Hospital (USTH) and Saudi German Hospital (22.4% and 15.5%, respectively). Most of participants had experience more than 5 years (63.8%) (Table 1).

Table 1. Characteristic of study subjects (n = 58)

Variable		Frequency (%)
Gender	Male	40 (69.0)
	Female	18 (31)
Job type	Radiology Technician	31 (53.4)
	Radiology Resident	5 (8.6)
	Radiology Consultant	22 (37.9)
Hospital	UST Hospital	13 (22.4)
	Saudi German Hospital	9 (15.5)
	Althawrah Hospital	8 (13.8)
	IbnSina Hospital	7 (12.1)
	Sab'een Hospital	5 (8.6)
	Police Hospital	5 (8.6)
	Alkuwait Hospital	4 (6.9)
	Others	7 (12.1)
Radiology Experience	Less than 2 Years	7 (12.1)
	From 2 - 5 Years	14 (24.1)
	More than 5 Years	37 (63.8)

The study showed that about 88% of the participants made 1 - 10 diagnostic errors 2013. These errors were classified to under-call (false negative) (29.3%), communication errors (27.6%), overcall (false positive) (25.9%), procedural complication (24.1%) and interpretation errors (15.5%). The most common causes of errors as mentioned by participants were unavailability of previous studies (37.9%) and inadequate clinical information (36.2%). Unfortunately, majority of radiologists (70.7%) did not keep records for their own errors (Table 2). Only 24.1% of radiologists had errors meeting in their departments. These meetings were perceived either both educational and blameless (50%) or blameless but non-educational (Table 3).

Table 2. Errors' frequency, classification, and causes

Variable	Frequency (%)
Keeping a personnel record for errors	
• Yes	17 (29.3)
• No	41 (70.7)
Number of errors made by participants in the last year	
• 1-10 errors	51 (87.9)
• 11-20 errors	2 (3.4)
• More than 20 errors	5 (8.6)
Classification of errors mentioned*	
• Overcall (false positive)	15 (25.9)
• Under-call (false negative)	17 (29.3)
• Interpretation errors	9 (15.5)
• Communication errors	16 (27.6)
• Procedural complication	14 (24.1)
Causes of errors mentioned*	
• Faulty of reasoning: The finding (lesion) was appreciated (known), but the wrong cause was written	5 (8.6)
• Lack of knowledge	14 (24.1)
• Under reading	11 (19.0)
• Poor communication	16 (27.6)
• Inexperience of staff	7 (12.1)
• Inadequate of facility	11 (19.0)
• Inadequate of clinical information	21 (36.2)
• Unavailability of previous studies	22 (37.9)

*The total of the answers are more than the sample size because participants can choose more than one answer

Table 3. Errors and their dealing (n = 58)

Variable	Frequency (%)
Having errors' meeting in the radiology department	
• Yes	14 (24.1)
• No	44 (75.9)
Attending 3 or more error meetings in the last year	
• Yes	13 (22.4)
• No	45 (77.6)
Describing the atmosphere of the errors meeting by participants *	
• Educational and blameless	6 (50)
• Educational but intense	1 (8.3)
• Blameless, but non-educational	3 (25)
• Uncomfortable with blame culture	2 (16.7)

*n= 14 patients who had meeting in their department, two participants did not answer the question

4. Discussion

The current study is an initial attempt to evaluate radiologists' perception of their own errors in Yemen. The study will help health system to build database on the diagnostic errors in radiology which has direct and indirect effect on patient safety. The study found that the most frequently errors run between one to ten errors. Similar findings have been reported from Karachi, Pakistan (9). Furthermore, Mankad and his colleagues reported that about 91% of radiologists made between one and 15 errors/year (4).

The present study showed that the under-call (false negative) had the higher frequency (29.3%). The predominance of under-call (false negative) which is also called perceptions errors has been previously reported from other countries (5, 9). In contrast, Mankad and his colleagues found that the majority of errors are due to overcall (false positive) (4). Under-call (false negative) interpretation of radiological findings is quite common which is due to wrong assessment of the abnormal findings. The underlying causes of such error are still debatable which may include biological, psychological and/or social factors (11).

This study found that unavailability of previous studies and inadequate of clinical information are the commonest causes of radiology errors. These findings could be due to masking the real findings by reading the previous report and clinical findings (12, 13). These results highlight the urgent need for establishing a good system for communication and recording in radiological practice (7). Unfortunately, majority of radiologists surveyed did not keep record for their own errors which are in agreement with previous study where only 20% of radiologists found to keep their own errors' record (4). Several possible reasons for the lack of errors' record have been reported including less awareness of radiologists to keep personal records, difficulty to define errors, absence of good quality system, moreover, and this process is quite tedious and time consuming (3, 4, 9).

The present study showed that most of radiology departments the surveyed do not organize radiology errors' meeting. Similar findings were reported by Saeed et al where 35% of radiologists only managed to attend errors' meetings. It is well known that establishing errors' meeting is an excellent opportunity for learning and quality improvement. It will create a comfortable environment to discuss error, its causes, methods of detection, and approaches of prevention (3, 4, 7, 9, 14).

Radiology workers who attended errors' meeting, in this study, perceived it in discrepancy manner. Some of them stated that it is educational and blameless and other perceived it as uncomfortable with blame culture. Many radiologists and other health care providers fear to attend errors' meeting which could be due to the approach of such meeting where it is a blameful with attributed to individual rather than healthcare system (4). Thus, it is highly recommended to make errors' meeting more effective by constructive criticism rather than blame culture and playing a role model by seniors to acknowledge their own mistakes and let others to learn from them (9, 15).

5. Conclusion

Radiology errors are still a significant problem affecting patient safety. Collaborative efforts must be established to educate radiologists about diagnostic errors in radiology and create a good environment for learning and improvement rather than blaming and embarrassing. This study has some limitations. They include small sample size

of participants and restrictions of study to Sana'a. Nevertheless, it will be the initial database for further studies in future to assess this issue.

Conflict of interest

The author declares that there is no conflict of interest.

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ORIGINAL ARTICLE

A Ten Year Descriptive Study of Adult Leukaemia at Al-Jomhori Teaching Hospital in Sana'a, Yemen

Jameel Al-Ghazaly[1,2,*], Waled Al-Dubai[3], Munasser Abdullah[4], Altaf Al-Mahagri[2], and Leila Al-Gharasi[2]

[1] *Department of Medicine, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen*

[2] *Hematology unit, Al-Jomhori Teaching Hospital, Sana'a, Yemen*

[3] *Department of Biochemistry and Cytogenetics, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen*

[4] *Al-Amana Specialized Laboratories, Sana'a, Yemen*

[*] **Correspondence author:**

E-mail: jameel_alghazaly@yahoo.com

Abstract:

Background: There is scarcity of data of the epidemiology of leukaemia in Arab countries including Yemen. Understanding patterns of leukaemia underpins epidemiology and can provide insight into disease etiology. The aim of this research is to determine the epidemiologic pattern of adult leukaemia in Yemen.

Methods: The research is a descriptive cross-sectional study. We analyzed the data of 702 adult patients with leukaemia, who were newly diagnosed over a ten-year period between October 1999 and October 2009 at the referral haematology centre in Sana'a at Al-Jomhori Teaching Hospital, according to type of leukaemia, age, sex, geographic distribution and time of diagnosis.

Results: Acute Myeloid Leukaemia (AML) was found to be the most common (45.1%) followed by Chronic Myeloid Leukaemia (CML) (26.5%), Acute Lymphoid Leukaemia (ALL) (17.7%) and Chronic Lymphoid Leukaemia (CLL) (10.7%), respectively. There was an almost equal prevalence of AML and CML for males and females but males had significantly more cases of ALL and CLL ($p = 0.008$). A significant variation in geographic pattern showed that the highest number of cases is seen the Central mountainous region and the least number of cases in the South-eastern region which is coastal and lowland ($p<0.001$). The seasonal variation showed that higher number of ALL cases was seen in the summer months (33%) compared with other seasons (21% in the spring, 24.2% in autumn and 21.8% in winter).

Conclusions: The pattern of adult leukaemia in Yemen is different from that seen in western countries which could be attributed to different environmental exposure. The geographic pattern indicates a possible role of certain environmental factors which warrant further investigations. The pattern of seasonal variation needs further studies for evaluating the seasonality.

Key words: Leukaemia, Yemen, Epidemiology, Seasonality, Geography, Environmental factors

1. Introduction

Cancer has been ranked the second after cardiovascular disease as leading cause of death from chronic diseases in developing countries. In 2007, deaths due to cancer in the developing world represented five of 7.5 million of the global cancer deaths. The World Health Organization (WHO) delivered a resolution calling for improved measures of cancer prevention, early detection and treatment in all WHO member countries (1). The Republic of Yemen lacks a national cancer register and there are no reliable data available (2). However, according to the first descriptive analysis report of the data on cancer cases in Yemen registered at the National Oncology Center during 2007, leukaemia was ranked as the third most common type of cancer after breast and Non-Hodgkin Lymphoma (Unpublished data).

The etiology of leukaemia remains unknown but it may be the result of a complex interaction between host susceptibility factors and different environmental susceptibility agents (3). The incidence of particular subgroups of leukaemia varies with age and sex which may suggest differences in etiology. The most common types of leukaemia in adults are AML, CML and CLL. In contrast, chronic leukaemia is extremely rare in childhood and ALL is the most common type of childhood leukaemia. Similarly all types of leukaemia show male predominance (4, 5).

Prior cancer chemotherapy and exposure to radiation and benzene are identified as risk factors for adult leukaemia, primarily AML (6). However these risk factors for adult leukaemia account for only a small proportion of all adult cases. Results of cytogenetic studies suggest that exposure to certain environmental agents may be associated with clonal chromosomal aberrations which may play a role in the activation of cellular oncogenes (7). Environmental risk factors that have been explored and have produced inconsistent association with leukaemia include farming, proximity to nuclear plants, hair dye, exposure to pesticides and petrol products, infections and alcohol consumption (6, 7). Life style factors including smoking, obesity and some dietary factors as risk for adult leukaemia have been assessed in several epidemiologic studies (8-13). Studies on the geographical distribution of leukaemia show higher number of patients of leukaemia who lived in rural areas which suggests that risk factors do exist in the rural environment (14-16).

Elucidation of environmental and life style risk factors requires understanding patterns of leukaemia which underpins epidemiology and can provide insight into disease etiology (17). Although Asian pattern including Japan, Singapore and Hong Kong were compared with American and European pattern, there is scarcity of data of the pattern of leukaemia in Arab countries including Yemen (17, 18). It sounds interesting to know the pattern of leukaemia in these developing countries which have different life style and different environmental exposure compared to that seen in the West or Far east countries (18). Yemen occupies the southern end of the Arabian Peninsula and has low standards of living similar to the situation in many developing countries. Malaria, schistosomiasis and intestinal parasites are common and visceral leishmaniasis is present in certain regions (19). Inadequate nutrition is also prevalent and Khat cultivation and regular khat chewing is very popular in the Yemeni community. In contrast, the situation is different in the West and other developed Asian countries where high standards of living are ensured and such parasitic infections are rare. The haematology unit at Al-Jomhori Teaching Hospital in the capital city Sana'a deals with haematological diseases including leukaemia and to which cases are

referred from all over Yemen (16, 19, 20). Thus, the aim of this research was to describe the epidemiologic pattern of adult leukaemia referred to this hospital over 10 years (October 2nd 1999-October 1st 2009).

2. Methods

Subjects

This descriptive cross sectional study included adult patients 14 years of age or older diagnosed for the first time as leukaemia between October 2nd 1999 and October 1st 2009 at the Haematology Unit at Al-Jomhori Teaching Hospital in Sana'a. Exclusions were patients who were previously diagnosed or have received treatment before presentation to the unit. The study was approved by Al-Jomhori Teaching Hospital authority.

Laboratory Investigations

The diagnosis of leukaemia was identified according to the standard practice and based on at least peripheral blood and bone marrow morphology and cytochemistry (19). Immunophenotyping, cytogenetic and molecular biology studies were done when needed for confirmation of the diagnosis (19). The patients were classified as AML, ALL, CML or CLL cases.

Data analysis

Data was analysed using SPSS version 10. The association between dependent and independent variables were tested using Pearson Chi-Square test. The significance level was considered at $p < 0.05$. The time of initial diagnosis of each case was recorded to assess for seasonal variation in the occurrence of leukaemia which is more objective than the time of initial symptoms which is subjective and cannot be determined accurately. However regarding acute leukaemia the presentation is usually within a short interval and moreover we categorized the time period according to seasons and not month-wise to accommodate for the possible delay of presentation. Regarding chronic leukaemia the symptoms are usually observed over a long period of time and season related variation in diagnosis is not expected and they are considered in analysis to serve as controls for acute leukaemia. Cases were distributed according to different geographical areas in Yemen (according to the governorates including patients resident in the towns and the districts officially following that governorate). The governorates were grouped into three regions (Figure 1). The Central mountainous region of the country includes the governorates of Sana'a, Dhamar, Almahweet, Marib, Ibb, Raymah, Al-Baydha and Ad-Dali. The Southern region includes the governorates of Taiz, Hadramawt, Al-Mahrah, Lahj, Abyan, Shabwa and Aden. The Northern region includes the governorates of Al-Hudaydah, Amran, Sa'adah, Hajjah and Al-Jouf. The population of Yemen according to the last Yemen's population census data of December 2004 was 19,721,643 (21). We used this census data, which is located at the midpoint of the study period, to assess the significance of variability of geographical distribution of leukaemia in Yemen. The population of the different regions (calculated by adding the total population of all governorates belonging to each region) was 8,317,650 for the Central region, 5,744,285 for the Southern region and 5,659,708 for the Northern region (21).

3. Results

Between October 2nd 1999 and October 1st 2009, 702 patients were included in this analysis. Of the total 702 patients, AML was the most common 45.1% (317/702), followed by CML 26.5% (186/702) and ALL 17.7% (124/702). CLL was least common 10.7% (75/702). The sex distribution of leukaemia shows a male/female ratio for all types 1.2:1, almost similar numbers of males and females for both AML and CML. For ALL and CLL, the diseases were more common

among males (table 1). The results are statistically significant (χ^2 = 11.858, p = 0.008).

Table 1. Prevalence and distribution of leukaemia in Yemen over 10 years according to gender

Sex	Types of Leukaemia n (%)*				Total
	AML	CML	ALL	CLL	
Male	159 (50.2)	95 (51)	80 (64)	49 (65)	383 (54.6)
Female	158 (49.8)	91 (49)	44 (36)	26 (35)	319 (45.4)
M/F ratio	1.0	1.0	1.8	1.9	1.2
Total	317 (45.1)	186 (26.5)	124 (17.7)	75 (10.7)	702 (100)

*Chi-Square test: χ^2 = 11.858, p = 0.008

Table 2 shows the age distribution of leukaemia. AML was most common in the 40-59 years age group, similar to CML. However for ALL, the disease is most common in the 14-19 years age group and CLL is most common in the elderly (≥ 60 years). The results were statistically significant (χ2 = 486.618, p<0.001).

Table 2. Prevalence and distribution Leukaemia over 10 years according to age

Age	Types of Leukaemia n (%)				Total
	AML	CML	ALL	CLL	
14-19	52 (16.4)	8 (4.3)	62 (50)	2 (2.7)	124 (17.7)
20-29	65 (20.5)	21 (11.3)	37 (29.8)	0 (0.0)	123 (17.5)
30-39	40 (12.6)	54 (29)	9 (7.3)	1 (1.3)	104 (14.8)
40-59	96 (30.3)	70 (37.7)	13 (10.5)	23 (30.7)	202 (28.8)
≥60	64 (20.2)	33 (17.8)	3 (2.4)	49 (65.3)	149 (21.2)
Total	317 (45.1)	186 (26.5)	124 (17.7)	75 (10.7)	702 (100)

*Chi-Square test: χ^2 = 486.618, p < 0.001

The median age [range] in years was 40 [14-90] for AML, 18.5 [14-75] for ALL, 40 [16-85] for CML, 60 [18-90] for CLL and 40 [14-90] for all types.

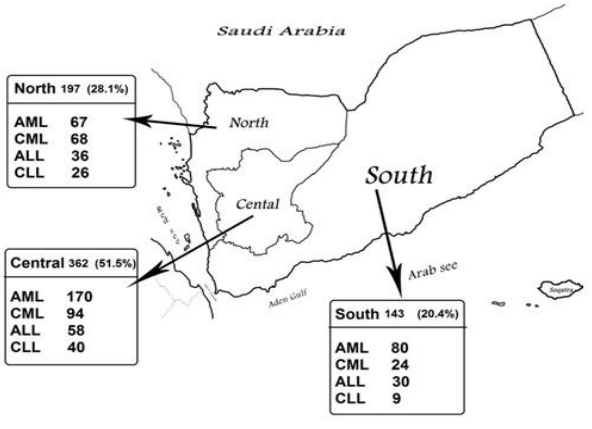
Table 3 shows the distribution of leukaemia cases according to the different seasons, spring (from 21 March to 20 June), summer (from 21 June to 20 September), autumn (from 21 September to 20 December) and winter (from 21 December to 20 March). No significant seasonal variation was noted when all leukaemia types were evaluated together (χ^2= 6.487, p = 0.69). When acute leukaemia types were evaluated separately, higher number of ALL cases was seen in the summer months (33%) compared with other seasons (21% in the spring, 24.2% in autumn and 21.8% in winter).

Table 3. Seasonal distribution of leukaemia cases in Yemen over 10 years

Season	Types of Leukaemia n (%)				Total
	AML	CML	ALL	CLL	
Spring	85 (26.8)	46 (24.7)	26 (21)	21 (28)	178 (25.3)
Summer	78 (24.6)	49 (26.4)	41 (33)	17 (22.7)	185 (26.3)
Autumn	69 (21.8)	37 (19.9)	30 (24.2)	17 (22.7)	153 (21.8)
Winter	85 (26.8)	54 (29)	27 (21.8)	20 (26.6)	186 (26.5)
Total	317 (45.1)	186 (26.5)	124 (17.7)	75 (10.7)	702 (100)

*Chi-Square test: χ^2 = 6.487, p = 0.69

Figure 1 is a schematic representation of a map of Yemen showing the geographical distribution of leukaemia cases. The Central mountainous region of the country had the highest number of leukaemia cases (362 patients) i.e. 51.5 % followed by Northern region (197 patients) i.e. 28.1 % .The least number of cases were seen in the Southern region (143 patients) i.e. 20.4 %. The Chi squared test showed a significant geographic distribution of leukaemia cases (χ^2 = 33.035, p<0.001).



Chi-Square test: χ2 = 33.035, p < 0.001

Figure 1. A schematic representation of a map of Yemen showing the geographical distribution of leukaemia cases in Yemen over 10 years (October 1999 to October 2009)

4. Discussion

This research is performed to study the epidemiology of leukaemia in Yemen. A total number of 702 cases of leukaemia were evaluated over the ten-year period (October 2nd 1999 to October 1st 2009). AML was most common followed by CML and ALL respectively and CLL was the least common constituting only 10.7% of the total number of leukaemia cases. This pattern is similar to that seen in Southeast Asia showing higher incidence of the myeloid leukaemia (AML and CML) and CLL is the least common (4, 5, 22). However, it is different from that seen in USA and other Western countries where CLL is the most common form of leukaemia (5, 22). This may indicate a different exposure to certain etiologic factors.

In this study there is a male predominance when all types of leukaemia were considered together with M/F ratio of 1.2. The male predominance is striking for ALL and CLL with M/F ratio of 1.81 and 1.88, respectively. However, there is an almost equal sex occurrence for AML and CML. The finding seen in the Western world is male predominance for all types combined and separately. The M/F in U.S. is 2 for CLL, 1.28 for ALL, 1.55 for AML, 1.73 for CML and 1.68 for all types (23). This may indicate a different environmental exposure for females in our community. Such suggestion has been raised by a study performed in United Arab Emirate where AML was significantly more common among national females (IRR: 1.93) (24). It was suggested that cumulative risk factors to which females could be exposed such as vitamin D deficiency as a result of sunlight deprivation and direct exposure to benzene and color enhancement in Henna (a herbal cosmetic used by Arab females to stain their nails, hands, feet a, legs and arms) may play a role in female predominance of adult AML incidence (24). Females in our community do share these two risk factors with other women in the Arabian Peninsula.

The age distribution of leukaemia is similar to the pattern seen in Western countries showing that AML cases increase with age, CML is a disease of the middle age, ALL is most frequent in the young and CLL is most common in the elderly group of patients. However for ALL, the second peak after 60 years of age was not seen in our study (4, 23). The median age for AML and CML in our study is 40 years compared to 64 and 60 years respectively in USA, 60 years in our CLL patients compared to 70 years in USA and it is 40 years for all types combined in our patients compared to 67 years in USA which means that our patients are in general 10 to 20 years younger which may indicate different age period during exposure to risk factors or that certain factors may delay the onset of leukaemia in Western patients (4, 22). A study on adult AML in UAE shows that the median age was 39 years which is similar to our patients indicating similar risk profile (24).

To the best of our knowledge, this is the first report in Yemen and even in the Arabian Peninsula and other Arab countries studying the geographic distribution of leukaemia. A distinct geographic pattern in the distribution of leukaemia was seen. Highest proportions of Leukaemia cases were observed in the Central region and the least number of cases were seen in the Southern region. This variation could be attributed to the habits of chewing Khat in the Northern and Central regions of Yemen considering that pesticides are used heavily for cultivation of khat to hasten its growth and consequently khat chewers are cumulatively exposed to pesticides which have been shown to be associated with leukaemia (25, 26). The adverse effects of chewing khat which is grown with

pesticides on human health were investigated in people of the mountainous areas of Yemen (27).

This study showed an increased number ALL cases in the summer compared to other seasons. This goes with other studies performed in western countries which provide evidence for seasonality and possible infectious etiology for ALL only (28-30). Further studies examining seasonality in developing countries including Yemen are recommended.

A limitation of this study is that it is a hospital based which may be affected by a referral bias which is influenced by variations in disease awareness, cultural barriers especially linked to the age and sex of the patient, inconvenience of travel and distance involved. However the fact that the study included cases during a ten year period may reduce the effect of referral bias (31). Such data are of importance providing an overview of the pattern of leukaemia in Yemen considering the fact that cancer registry has not been implemented yet in Yemen.

5. Conclusion

In conclusion, the epidemiology of leukaemia in Yemen looks distinctive concerning the finding of equal sex incidence of AML and CML. A geographical variation of distribution was documented with more Leukaemia cases in the Central region and the least number of cases is seen in the Southern region. Higher cases of ALL were recorded in the summer. The current study warrant further studies to identify the environmental and life style risk factors of leukaemia in Yemeni population to help development and implementation of protective strategies.

Conflict of interest

The authors have no conflict of interest to disclose.

Author's Contribution

JA designed the study; JA, WA, MA, AAM, and LA contributed to data collection and Laboratory analysis; JA and WA contributed to data analysis and the interpretation of results. JA drafted the manuscript. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Environmental Hazards as a cause of Pediatric Intensive Care Admission

Haidar N. A.[1,*]

[1] *Pediatric department, University of Science and Technology Hospital, Sana'a, Yemen*

[*] **Correspondence author:**
E-mail: haidarnaa@yahoo.com

Abstract:

Background: Children are exposed to several environmental hazards with variable effects from mild to severe manifestations leading to death. The aim of this study is to study the pattern of Pediatric Intensive Care Unit (PICU) admission due to environmental hazards and its mortality rate.

Methods: This is a hospital-based study conducted during a 5 years period in Al-Madinah Al-Munwarah, Saudi Arabia.

Results: Out of total PICU admissions, 9% were due to environmental hazards. Bronchial asthma which is triggered mostly by environmental factors, was the most common (35.3%) followed by: trauma (27%), poisoning (15.3%) and submersion injuries (9.7%). Males were significantly more exposed to environmental hazard than females ($\chi 2= 13$, $p = 0.021$). Statistical analysis showed a significant difference in the frequency of environmental hazards between summer and winter ($\chi 2= 12$, $p = 0.033$). Trauma, poisoning, submersion injuries, stings and bites were more in summer compared to winter. However, bronchial asthma had higher frequency in winter. The Median length of PICU stay ranges from 1.6 – 12.5 days depending on the type of hazard. Overall mortality rate was 8.8% with the highest rate among trauma followed by submersion injury patients with no fatality in drug ingestion or food poisoning.

Conclusion: Environmental hazards represent a preventable major health problem with significant mortality and burden in health economics by long PICU stay and its sequel.

Key words: Environmental hazards, Admission, PICU, Mortality

1. Introduction

Environmental hazards can be chemical, physical, mechanical, biological and psychosocial. The patterns of illness in pediatric population in the developing countries can be considered in the double burden category where the emerging pattern of civilization of chronic disabling health problems is increasing and the communicable diseases still exist in a significant prevalence (1). Environmental hazards are among the contributing etiologies for this double burden. The United Nations Environment Programs (UNEP) and World Health Organization (WHO) are taking in consideration these changes (2).

In developed countries, the communicable diseases have dramatically declined while the diseases of environmental origin are increasing which warranted the establishment of the Children's Environmental Health Network (CEHN) in USA (3). The child environment starts primarily at home then extend to outdoor. It has been estimated that 25-33% of the global burden of diseases can be attributed to environmental risk factors. Children under 5 years of age seem to bear the largest environmental burden (4). The spectrum of environmental hazards is so wide ranging from simple transient trigger of bronchial asthma and other respiratory diseases (5) to life threatening events (6, 7), going through structural and DNA changes (8-13) leading to lifelong effects. In spite of the known wide spectrum of environmental hazards, their impact on the pediatric intensive care (PICU) is not well known, particularly in the Arabian Peninsula. Thus, the objective of this study was to identify the pattern of admission to the PICU due to the environmental hazards and the magnitude of this problem and its contribution to the mortality rate.

2. Methods

Subjects

A retrospective hospital-based study was conducted in the Madinah al-Munwarah, Saudi Arabia. All the cases admitted to the pediatric intensive care unit (PICU) due to environmental hazards were identified from the admission and discharge log book in the PICU. The study included the cases admitted during a 5 years period from 2007 to 2011. The medical charts were reviewed for age, sex, nationality, type of hazard, length of PICU stay, and outcome. Because of the ill-defined clear demarcation between the four seasons, the year was divided into two periods to encompass the two main climate changes in the area which are the summer (May till October) and the winter (November till April).This study was approved by the hospital ethical committee.

Data analysis

The data were collected in excel sheet and cross-checked for accuracy. Data analysis was performed by using Statistical Package for Social Sciences for Windows (SPSS) version 21. Association between variables was tested using Pearson Chi-Square test where applicable.

3. Results

During the study period, there were 216 patients admitted to the PICU due to or triggered by the environmental hazards, which represented about 9% of the total admission to the PICU. Of the 216, 127 (60%) were males and 68 (40%) were females. The median of age was 3.7 months with inter quartile range (IQR = 0.1 – 10.8). These hazards included bronchial asthma (35.3%); trauma (26.9%); poisoning (15.3%); submersion injuries (9.7%); miscellaneous (6.9%); and bites and stings (5.9%). The Median of length of stay in the PICU ranges from 1.6 - 12.5 days depending on the type of hazard (Table 1). Trauma was

commonly due to Road Traffic Accident (RTA) (77%) followed by fall (21%) with 80% of these events being affected the head. Poisoning included drug ingestion (9.3%), Carbon monoxide (3.7%) and food (2.3%). Bites and stings included scorpion stings (4.6%) and snake bites (1.3%). Miscellaneous included strangulation (2.8% and all were males), burn (2.8%); mostly males and caused by flames with one electrical burn, and foreign body aspiration (1.3%) with mean age of 27 months.

Table 1. Frequency of environmental hazard leading to PICU admission, median age and length of stay in the PICU (n = 216)

Type of hazard	Frequency n (%)	Age Median (IQR)	PICU Los © Median (IQR)
Bronchial asthma	76 (35.3)	2.5 (1.5 – 7.5)	2.0 (1.0 – 3.80)
Trauma	58(26.9)	3.8 (1.6 – 5.8)	3.5 (2.0 – 13.8)
Poisoning ◊	33(15.3)	2 (0.10 – 7.0)	1.6 (0.9 – 4.6)
Submersion injuries	21(9.7)	2.5 (1.7 – 7.0)	2 (1.0 – 20.0)
Snake bites and scorpion stings	13(5.9)	5.5 (0.79 – 8.8)	1.6 (0.4 – 3.0)
Miscellaneous *	15(6.9)	6 (2.5 – 10.8)	12.5 (3.4 – 20)

© PICU Los: Length of stay in Pediatric Intensive Care Unit
◊ Poisoning included: Drugs, Foods, Carbon-monoxide.
*Miscellaneous included: Burn, Strangulation, Foreign body aspiration.

This study showed that males are more exposed to submersion injuries, bronchial asthma and miscellaneous compared to females. However, females had higher proportion of Scorpion stings and snake bite. The difference between males and females in the exposure to the environmental hazards was statically significant ($\chi 2$= 13, p= 0.021) (Table 2).

Statistical analysis showed a significant difference in the frequency of environmental hazards between summer and winter ($\chi 2$= 12, p= 0.033). Trauma, poisoning, submersion injuries and stings and bites were more in summer compared to winter. However, bronchial asthma had higher frequency in winter (Table 3). The overall mortality rate was 8.8% with the highest rate among trauma followed by submersion injury patients but no fatality in drug ingestion or food poisoning (Table 4).

Table 2. Sex distribution of patients admitted to the PICU due to environmental hazard

Type of Hazard	n	Males n (%)	Females n (%)
Bronchial asthma	75	49 (65.3)	26 (34.7)
Trauma	57	28 (49.1)	29 (50.9)
Scorpion stings and snake bite	13	5 (38.5)	8 (61.5)
Poisoning ◊	33	17 (51.5)	16 (48.5)
Submersion injuries	21	16 (76.2)	5 (23.8)
Miscellaneous*	14	12 (85.7)	2 (14.3)

◊ Poisoning included: Drugs, Foods, Carbon-monoxide.
*Miscellaneous included: Burn, Strangulation, Foreign body aspiration.
$\chi 2$= 13, P = 0.021

Table 3. Seasonal variation among patients admitted to the PICU due to environmental hazard

Type of hazards	N	Summer N (%)	Winter N (%)
Bronchial asthma	75	32 (42.7)	43 (57.3)
Trauma	57	36 (63.2%)	21 (36.8%)
Poisoning	32	21 (65.6%)	11 (34.4%)
Submersion injuries	21	16 (76.2%)	5 (23.8%)
Scorpion stings and snake bite	13	9 (69.2%)	4 (30.8%)
Miscellaneous	14	8 (57.1%)	6 (42.9%)
Total	212	122 (57.5)	90 (42.5)

$\chi 2$= 12, P = 0.033

Table 4. Mortality rate among patients admitted to PICU due to environmental hazard

Type of Hazard	Total number of patients	Mortality rate n (%)
Bronchial asthma	76	1 (1.3)
Trauma	58	9 (16)
Submersion injuries	21	5 (24)
Drug poisoning	20	0 (00)
Scorpion stings	10	0 (00)
Carbon monoxide poisoning	8	1 (13)
Strangulation	6	1 (17)
Burn	6	1 (17)
Food poisoning	5	0 (00)
Snake bites	3	0 (00)
Foreign body aspiration	3	1 (33)
Total	216	19 (8.8)

4. Discussion

This study was conducted to identify the pattern of admission to the PICU due to the environmental hazards. In this study asthma was the most common cause of admission to PICU among the environmental related hazards which was not surprising. There is a consistent and strong association between childhood hospital admission due to asthma exacerbation and outdoor air pollution independent of any temperature variation (16). Asthma could be triggered by a verity of pollutants which stimulate an acute attack, including tobacco smoke, traffic-related pollution, synthetic bedding and furry pets, particle components as in diesel and gasoline exhaust and wood smoke (17-21).

Childhood injuries were widely studied in the primary care (22), but less in intensive care setting. The reported usual causes of trauma are RTA as the most common cause followed by water related injuries, and burn with variations according to the age groups (23) which is consistent with the pattern of incidence in this study. In infants, falls incidence was reported to be the most common followed by ingestion and burn (23). However, in this study, trauma due to RTA was predominant, highlighting RTA as a major health problem in the region. Other causes were reported to be significant as Bicycle-related injuries among children 5 years or older, with a majority suffered from head and skull injuries (25, 26). The head injury was the most common type of injury in this study which could be explained by the importance of admitting these patients to the PICU not necessarily for intervention but could be only for close observation compared to most of the other body parts trauma. The age pattern of the strangulation subgroup was similar to previous studies but none occurred in a school which is not in agreement with other reports (27, 28).

Burn patients showed a similar sex distribution but higher age group and difference in the underlying cause of burn compared to other studies which showed the majority as scald burn (29, 30). Electrical injury reported to be predominantly in young children with high mortality and morbidity rate (31, 32). In this study there was only an eight years old child who suffered this event in a garden due to exposed electrical wire resulted in significant morbidity.

The majority of poisoning conditions in this study were accidental caused by drugs and carbon monoxide with younger age, which is similar to several other studies (33, 34). The effect of drug ingestion varies from mild to severe manifestations (35, 36). However, no significant sequel from drug ingestions, snake bites and scorpion stings was noted in this study, which could be due to the rapid access to health care services, which was not the case in other reports (37).

The majority of submersion injuries took place in swimming pools similar to previous studies (7). Submersion injuries are still representing a significant health problem because water safety practices were lacking in most cases as evidenced by the fact that most of the victims were not properly supervised at the time of swimming (7). In our patients with foreign body aspiration was of similar sex and age pattern to previous reports (38), and formed the highest rate of mortality.

The seasonal variation in trauma; asthma; drug poisoning; snake bite and scorpion sting, were all previously reported (39-43). The significant difference in the higher summer incidence in trauma, poisoning, submersion injuries and stings and bites, could be explained by the longer time of outdoor exposure and free playing time with may be less parental supervision during school vacation.

The overall mortality rate from the environmental hazards admitted to the PICU was higher than the mortality rate among all PICU admissions. In this study, trauma was the most common cause of death followed by submersion injuries both forming 73% of the mortalities due to the environmental hazards. There were no deaths in drugs ingestion, and food poisoning, similar to previous studies (44). Though scorpion stings were a known cause of mortality due to heart failure and pulmonary edema (45), there were no deaths in our study which could be explained by small number of cases and rapid access to health care services. This loss of life's in combination with long PICU stay, that lead to loss of expenses, represent an important burden to the health care services with a special concern being a preventable problems.

5. Conclusion

Environmental hazards represent a major health problem particularly during summer in most of these hazards with significant mortality and burden in health economics by long PICU stay. These hazards are avoidable. Thus, preventive measures should be implemented to reduce these hazards such as organizing educational programs in schools prior summer vacation.

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ORIGINAL ARTICLE

Preparation of Alginate Microspheres for the Delivery of Risperidone

Al-Tahami K.[1,*]

[1] *Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Science and Technology, Sana'a, Yemen*

[*] **Correspondence author:**
E-mail: k.altahami@ust.edu

Abstract:

Aim: The aim of this research is to prepare and evaluate alginate microspheres of prolonged delivery of a model drug, Risperidone.

Methods: Alginate microspheres containing Risperidone were prepared employing cross-linking method by calcium chloride. The formed microspheres were evaluated for percentage yield, drug content, drug loading, and encapsulation efficiency. In vitro release studies were carried out in phosphate buffer (pH 7.4).

Results: The formed microspheres exhibited good drug loading and encapsulation efficiency. The drug release was sustained over a period of 8 hours.

Conclusions: The fabricated Risperidone microspheres showed extended drug release, which could improve the therapeutic agent bioavailability and increase patient compliance. The delivery system developed can potentially serve for the delivery of many therapeutic agents.

Key words: Alginate, Microspheres, Sustained release, Risperidone

1. Introduction

Conventional therapeutic systems, though cheap and easy to manufacture, show many therapeutic problems including fluctuating plasma levels, inadequate activity, and poor compliance by patients due to the repeated dosing. Furthermore, conventional dosage forms are unpredictable and erratic; in many cases, a high amount of drug is required to guarantee that the effective concentration of drug is eventually achieved at the site of action. The pharmacokinetic parameters of the therapeutic agent are governed solely by drug's physicochemical properties, which are not always optimal (1).

Sustained drug delivery systems release encapsulated drugs in a prolonged fashion to maintain an effective therapeutic concentration for an extended period of time (2). Sustained drug delivery formulations often improves drugs' efficacy. In addition, drug reservoirs in sustained drug delivery systems protect the encapsulated therapeutic agents from possibly harsh physiological conditions and thus improve drug's stability and duration of action.

Microspheres are multiparticulate drug delivery systems that can be prepared by various methods and are used for the sustained delivery of drugs (3). They could be injected into the body due to their small size. This eliminates the need to surgically implant long-acting drug delivery reservoirs. Biocompatibility of the polymer and its degradation products is crucial for biomedical use (4). Moreover, the ability of the body to degrade/eliminate polymeric systems is favoured for drug delivery, since this opts out the need for surgical removal of the delivery system once the drug is depleted (5).

Many natural and synthetic polymers were investigated for their use in drug delivery. Alginates, natural polymers found in brown algae, have been investigated for the controlled drug delivery (6-9). Alginates consist of chains of mannuronic acid, guluronic acid, and mannuronic-guluronic. Alginate's safety is well-established and offers a further protective effect on the viability of mucous membranes of the gastrointestinal tract (6).

Risperidone is an antipsychotic agent, which belongs to the benzisoxazole family. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. The active forms of the drug are both Risperidone and its active metabolite 9-hydroxy Risperidone. Risperidone is used for the treatment of schizophrenia and is widely accepted because Risperidone causes less motor activity depression than classical neuroleptics (10). Yet, as with most of antipsychotic therapeutic agents, patient incompliance is still one of the major reasons for therapy failure.

The aim of this work is to formulate alginate microspheres for the sustained delivery of a model drug, Risperidone.

2. Methods

Materials

Risperidone was procured as a gift from the Jordanian Pharmaceutical Manufacturing company JPM (Amman, Jordan).Sodium alginate was purchased from B.M.S (Italy).All chemicals used were of analytical grade and were used as received.

Preparation of microspheres

Risperidone containing microspheres were prepared by cross-linking technique with minor modifications (11, 12). Different concentrations of sodium alginate were dissolved gradually in distilled water (3% and 1.5%) and homogenized for one hour. Drug polymer solution was prepared by dissolving 200mg of drug slowly into formerly prepared alginate solution with constant mixing for 30 minutes. Five grams of calcium chloride were dissolved in 100 ml of distilled water to prepare the gelation medium. The drug-polymer solution was then extruded through glass syringe into the gelation medium. The agitation was carried out by propeller at 200 rpm.

After one hour, 2 millilitres of isopropyl alcohol were added drop wise to harden the formed microspheres (13, 14). After 10 minutes, the microspheres were collected by filtration and washed with deionized water. The microspheres were dried at 45ºC until they attained constant weight.

Characterization of microspheres

- Percentage yield

The Risperidone-containing microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula (15):

Percentage yield = {microspheres mass/ mass of polymer + drug}*100

- Drug content

The different prepared formulations were assayed for drug content. Microspheres samples were weighed and powdered. Then they were dissolved in of phosphate buffer. The drug content was determined by measuring the UV absorbance at 280 nm (16).

- Encapsulation efficiency and drug loading:

Encapsulation efficiency and drug loading of formed microspheres were determined employing the following equations (15):

Encapsulation efficiency = (Experimental drug mass in sample/ Hypothetical drug mass) * 100

Drug loading = (Drug mass in microspheres / Microspheres sample mass) * 100

In vitro drug release

The release of the drug from the alginate microspheres was determined in phosphate buffered saline solution (PBS, pH 7.4). The alginate microspheres (15 mg) were suspended in 1 mL of PBS. The samples were incubated at 37±0.5°C with continuous shaking (50 rpm). At predetermined time intervals, the sample was withdrawn and centrifuged at 2000 rpm for 5 min. The supernatant was collected and assayed for drug release (17).

3. Results

Two different formulations were prepared varying in polymer concentration (Table 1). The percentage yield of both formulations was found out to be 78.6% and 59.9% respectively (Table 2). Higher drug content (and hence, percentage yield) was observed in formulations containing 1.5 % alginate polymer.

Table 1. Composition of alginate microspheres

Formulation	Alginate concentration	Drug content (mg)	Drug: Polymer ratio
F1	1.5%	200	1:7.5
F2	3.0%	200	1:15

Table 2. Drug content and percentage yield of different formulations

Formulation	Theoretical drug content (mg)	Actual drug content (mg)	Percentage yield (%)
F1	200	113	78.6
F2	200	87	59.9

Table 3 shows the results of drug loading and encapsulation efficiency. Increasing drug to alginate ratio increased percentage of loading. Formulations exhibited good encapsulation efficiencies of 71.97% and 72.63% for formulations containing 1.5% and 3% polymer concentration, respectively.

Table 3. Drug loading and encapsulation efficiency of microspheres

Formulation	Drug Loading (%)		Encapsulation efficiency (%)
	Theoretical	Actual	
F1	11.76	8.45	71.97
F2	6.25	4.54	72.63

Phosphate buffer (pH 7.4) was used for in vitro release studies. Figure 1 shows the cumulative release of Risperidone from alginate microspheres in phosphate buffer. The drug release was prolonged for up to 8 hours in formulations containing 1.5% and 3% polymer concentration.

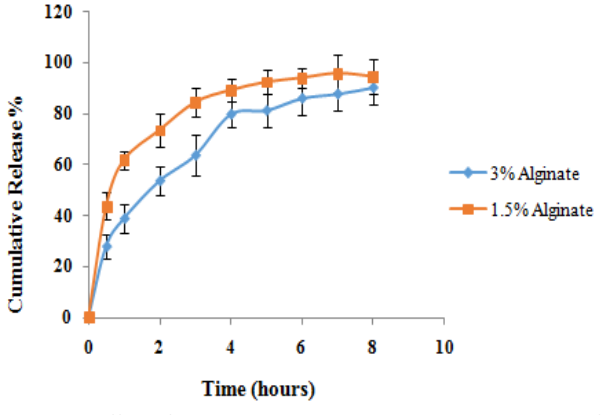

Figure 1. Effect of polymer concentration on the in vitro release of Risperidone

4. Discussion

The high percentage yields obtained in our study confirm that this delivery system was suitable for the formulation of Risperidone microspheres. Higher percentage yield was observed for formulations containing higher drug to polymer ratio. These findings comply well with results reported in other studies (15).Table 3 shows the effect of alteration of with polymer: Risperidone ratio on drug loading and encapsulation efficiency. Higher loading was achieved by increasing the percentage of Risperidone with respect to alginate.

Risperidone release from polymeric spheres can be explained by two mechanisms. The drug is released by diffusion from the encapsulating alginate microspheres. Secondly, the drug leaches out from the microspheres through the erosion and/or degradation of the matrix. The latter phenomenon could be attributed to the removal of the cross-linker, calcium, from the microspheres (18). The swelling of alginate molecules increases matrix porosity and thus increases both diffusion and erosion. These findings comply well with the higher drug to polymer ratio used in formulation F1 (19). Phosphate buffer has a chelating action due to the phosphate ions which helps further in the disruption of the matrix. Both of our formulations exhibited a sustained release of Risperidone over a period of 8 hours. A slower release pattern was observed for formulation containing higher amounts of the polymer. Similar results were obtained for verapamil loaded microspheres reported in a previous study (20). It was shown that drug release could be extended by increasing polymer proportion. Similarly, insulin and diaminopyridine microparticles were successfully prepared by solvent evaporation method and drug to polymer ratio was shown to affect microspheres characteristics and drug release profile (21, 22).

5. Conclusion

Alginate-based microspheres of Risperidone were successfully prepared and separated by cross-linking method. The formed microspheres showed good percentage yield and encapsulation efficiency. Drug release studies carried out in vitro showed prolonged release of Risperidone from both formulations employing phosphate buffer as a release media. Slower drug release was observed with increasing the polymer concentration. High burst release of Risperidone was observed in all formulations. It was feasible to prepare alginate-based microspheres capable of extending drug release over a period of time.

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ORIGINAL ARTICLE

Comparative Analysis of Five Brands of Lisinopril Tablets in Yemeni Market

Othman G.Q.[1,*]

[1] *Department of Pharmaceutical science, Faculty of pharmacy, University of Science and Technology, Sana'a, Yemen*

[*] **Correspondence author:**
E-mail: gamilqasem@yahoo.com

Abstract:

Background: In poor countries such as Yemen, the cost of drugs is a factor affecting the patient's decision to buy it and generic medicines are introduced as cheaper alternatives to the high cost brands. However, it has been believed that generic medicines are inferior in quality compared to the branded medicines. Thus, the aim of the present study is to investigate the physicochemical equivalence of five brands of tablets containing Lisinopril (antihypertensive) sourced from different retail pharmacy outlets in the Yemeni market.

Methods: The quality and physicochemical equivalence of five different brands of Lisinopril tablets were assessed. The assessment included the evaluation of uniformity of weight, friability, crushing strength, disintegration and dissolution tests as well as chemical assay of the tablets.

Results: Results obtained showed that all five brands of the Lisinopril 5 mg tablets passed the British Pharmacopoeia (BP) standards for uniformity of weight, the crushing strength/hardness test and the friability test. All the brands passed the disintegration test and standard assay of content of active ingredients

Conclusion: The five brands of Lisinopril 5mg tablets that were analysed passed all the BP quality specifications and were physically and chemically equivalent. All tested formulations were found to be equivalent.

Key words: Lisinopril, Brands drugs, Uniformity of weight, Disintegration, Friability, Hardness

1. Introduction

The increasing numbers of generic drug products are available in the market making it possible for people involved in providing healthcare services to select a particular generic drug from several supposedly equivalent products(1). Internationally the use of generic drugs is steadily increasing resulting from rising cost on drug budgets. Major savings in health care expenditure is possible by using generic drugs as they are usually cheaper than the innovator brands. However, physicians have doubt on the quality of generic drugs (2, 3) and their reliability as well as interchange of certain drug categories (4). Generic medicines are widely believed as inferior in their therapeutic efficacy and quality to branded products (5, 6) even though they are bio-equivalents of their innovator counterparts and are produced under good manufacturing practices (7).

Countries in Central and Eastern Europe and the Independent countries emerging from the former Soviet Union reported that manufacturers of imported branded medicines are promoting that generic drugs are inferior in quality as compared to the branded ones (8). In order for a generic drug to gain approval from FDA, it must be similar to the innovator drug in active ingredients, strength, dosage form, route of administration, the same usage indications, bioequivalent meet, batch requirements for identity, purity, quality and be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products (9).In Yemen, which is considered a poor country, the cost is the decisive factor in determining the patient access to health care. Many people put off the use of medications they need because of its affordability and the high cost of branded drugs. Under these circumstances, locally manufactured medicines are offered as alternative since they are cheaper. The objective of this study is to assess the quality of these five brands of Lisinopril tablets that are commercially available in the Yemeni market.

2. Materials and Methods

Samples

Five commercial products (brands) of Lisinopril, labelled to contain 5 mg per tablets, from different manufacturers were purchased and coded as A, B, C, D and E and then separated (Table 1). Various analytical methods and tests which are important for the development and manufacture of pharmaceutical formulations (10) were performed for all the tablet brands of five formulations in the study.

Table 1. Country of origin, manufacture and expiry dates of five brands of list tablets

Country	Brand	Code	Strength (mg)	Exp. Date
Sweden	Zestril®	A	5mg	12 \ 2014
Yemen	Lotensin®	B	5mg	1\ 2014
Yemen	Lisistril®	C	5mg	1 \ 2013
Jordon	zenoril®	D	5mg	7 \ 2014
India	cipril®	E	5mg	12 \ 2013

Weight Variation Test

The variation of the weight of individual tablet is a valid indication of the corresponding variation in the drug content. Controlling tablet weights within a tight range will contribute to better tablet hardness and friability (11). The acceptable limit for the deviation of weight for tablets having average weight of 250 mg or more should not exceed 5% (12). Ten tablets were selected from each of the brand and weighed individually using electronic balance (Kern, Germany, Model: D-72336). Their average weights were calculated. For all tablet brands following mathematical equation was used for weight variation (13):

Highest weight variation = (Highest weight − Average weight/Average weight) × 100

Lowest weight variation = (Lowest weight − Average weight/Average weight) × 100

Hardness test

Hardness indicates the capability of a tablet to withstand mechanical shocks during handling in manufacturing, packaging and shipping (14). The acceptable value of hardness or crushing strength of tablet is 4kg or more (15). During the study, hardness of all tablets was determined using Tablet Breaking Force Tester, Germany (PHARMA TEST: PTB). For all of the formulations, five tablets of each brand were taken and hardness of the tablets was determined.

Friability test

Friability test is essential to evaluate the ability of a tablet to withstand abrasion in packing, handling and transporting. In the study, it was determined using PHARMA TEST: PTB. Friabilator (Germany). The value of friability was expressed in percentage (%). Ten tablets for each brand were initially weighed and transferred into friabilator which was operated at 25 rpm for 4 minutes (up to 100 revolutions). The tablets were weighed again and the percent of friability was then calculated by using the following formula (13):

% Friability = (Weight before test − Weight after test/Weight before test) × 100

Generally the considerable range of weight loss of conventional compressed tablet is less than 0.5 to 1% (14).

Disintegration time test

Disintegration is the break down process of tablet into smaller particles and is the first step towards dissolution. The standard disintegration time for USP uncoated tablet must be as low as 5 minutes but majority of the tablets have a maximum disintegration time of 30 minutes (14). The method specified in the USP/NF (1980) was used (PHARMA TEST: PTZ S). The volume of disintegration medium used was 100 ml of 0.1N HCl and the temperature was maintained at 37±1°C throughout the experiment for each tablet of all the brands. Six tablets of each brand were selected and placed in each of the cylindrical tubes of the basket and the disc was used. The time taken to break each tablet into small particles and pass out through the mesh was recorded. Mean disintegration time was calculated for each of the brands (16).

The dissolution rate test

Generally dissolution test is carried out to determine drug release pattern during a specific period of time (17). Dissolution test for each of the tablet brands was performed using Dissolution Tester – Germany (PHARMA TEST: D-63512). 900 ml of phosphate buffer, pH 2 was used as dissolution medium. The process was done at a speed of 50 rpm by maintaining temperature at 37±1ºC in each test. Samples were withdrawn as 5 ml at a regular time intervals of 10 minutes which was predetermined and same procedure was continued up to 30 minutes by replacing equal amount of fresh dissolution medium (phosphate buffer, pH 2). The filtered samples were suitably diluted and analyzed using HPLC at 215 nm for Lisinopril. By measuring the absorbance, the percentage of drug release was calculated (17, 13). All measurements were conducted in triplicate.

Content of uniformity test

The content uniformity of the active ingredient in tablets was carried out by HPLC (Shimadzu CLharASS-VP V6.12 SP3, Kyoto, Japan). The mobile phase consisted of (Mono basic phosphate buffer: Acetonitrile) (80:20) pH=2.0. The flow rate was 2.0 ml/min, the injection volume 20 µl and the detection wavelengths 215 nm (Lisinopril). ODS

hypersil C18 Column (25cmx4.6mm packed with 10 µm silica) was used throughout the experiments. Chemical identification test and content of active ingredient uniformity test were conducted according to the standard method in BP 2002.

Data Analysis

Data for weight uniformity test, friability, crushing strength and the disintegration and dissolution times of the tablets were analyzed by determining the mean ± standard deviation.

3. Results

All the samples used for the study were within their shelf life at the time of investigation. The results of the physicochemical properties of the various brands of Lisinopril are presented in Table 2 and 3.

The uniformity-of-weight determination for the brands Lisinopril tablets gave values that comply with the British Pharmacopoeia specification (not exceed 5% deviation). It was found that A, B, C, D and E brands of Lisinopril group passed the test of tablet crushing strength or hardness. All Lisinopril brands showed friability values ranging from 0.18 to 0.29% (Table 2).

Table 2. Results of unofficial quality control tests conducted on the Lisinopril tablets

Code	Weight uniformity test, mg Mean (± SD)	Crushing Strength Kgf Mean (± SD)	Friability Mean (± SD)
A	106.3 (0.9)	4.61(0.195)	0.188 (0.111)
B	99.12 (1.8)	7.92 (0.608)	0.202(0.022)
C	101.2 (2.5)	3.93 (0.452)	0.494(0. 0111)
D	91.04 (2.2)	5.61(1.558)	0.231(0.192)
E	137.4 (2.7)	4.12(0.564)	0.291(0.142)
LIMITS		>4 kg/cm^2	<1%

The overall disintegration time for Lisinopril tablet brands was in the range from 15 seconds to 7 minutes and 50 seconds. It was observed that all the samples passed the dissolution time as specified in the official standard. All the samples passed the potency or active content tests as specified in the official standard (Table 3).

Table 3. Results of official quality control tests conducted on the Lisinopril Tablets

Code	Disintegration Time (min) Mean (± SD)	Dissolution after 30 min Mean (± SD)	Active Content Uniformity test Mean (± SD)
A	0.67 (0.102)	101.03 (1.04)	110.8 (1.414)
B	0.25 (0.012)	103.7 (0.496)	110.4 (2.969)
C	5.36 (0.313)	96.67 (4.21)	106.65 (6.611)
D	7.50 (0.504)	103.43 (1.193)	106.87(2.142)
E	4.44 (0.455)	99.68 (3.751)	102.8 (1.555)
LIMITS	< 15	>70%	95-105%

4. Discussion

Five different brands of Lisinopril tablets obtained from different retail pharmacy outlets within Sana'a Yemen were subjected to a number of tests in order to assess their quality control. The uniformity of weight determination for all the brands showed compliance with the official specifications (B.P 2002), as none of the brands deviated by up to 5% from their mean. A variation beyond the pharmacopoeia limits indicates unacceptable products (18). All the brands gave less than 0.5%w/w loss in weight with the friability test determination, which is less than the official specification of 1%w/w (B. P. 2002), showing that all the brands could withstand abrasion without loss of tablet integrity. Adequate tablet hardness as well as reasonable friability is required for consumer acceptance (19). The mean crushing strength determination which is a measure of the degree of hardness of the tablets gave the values between 7.92 and 3.93 kgcm-2. Although, the crushing strength is not an official

method of assessing tablet quality, it is still useful in assessing the integrity of tablet dosage forms (20). All the brands passed the disintegration test according to the specification of BP criteria. The B.P. specifies that not less than 70%w/w labeled content should dissolve at 45minutes. The result obtained from this study revealed that five of the brands achieved more than 96% at 30 minutes. The obvious implication of this is that the five brands may exhibit good bioavailability profile in vivo. Dissolution rate has been reported to have a direct bearing on the bioavailability profile of tablet dosage forms as it can be used to predict the drug release pattern in vivo (21).

According to the United State Pharmacopeia (USP), a Lisinopril tablet should contain not less than 90% and not more than 110% of Lisinopril. The percentage contents of the analyzed sample tablets using HPLC ranges from 102.8 to 110.8. This study was comparable with other studies which demonstrated brand-brand equivalence with the innovator product (22, 23). On the other hand, A study on 85 generic products from 21 countries reported that 91% of the generic piroxicam products evaluated failed to meet the routine in vitro USP quality assurance criteria for potency and or dissolution (24). This difference in dissolution could result in altered bioavailability and hence potency, which may result in therapeutic failure. As well as this study in contrast with latest study (25) which was conducted in Nigeria to compare between different brands of Lisinopril tablet using HPLC and UV Spectrophotometer.

5. Conclusion

All the brands complied with the official specification for uniformity of weight, hardness and disintegration. In general, the tablets showed good friability profiles, since most had friability values of less than 1.0%. The various brands were chemically equivalent because all had chemical content not less than 90% and not more than 100% (w/w).

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Conflict of interest

The author declares that there is no conflict of interest.

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CASE REPORT

Complete Disruption of the Left Main Bronchus due to Blunt Chest Trauma

Aldahmashi M. N.[1,2,*]

[1] *Cardiothoracic Surgery, Thamar University, Yemen*
[2] *Cardiothoracic Surgery, UST Hospital, Sana'a, Yemen*

[*] **Correspondence author:**
E-mail: dahmashi@hotmail.com

Abstract:

Isolated tracheobronchial disruption is an uncommon injury usually associated with severe blunt thoracic trauma. We herein report a 14 year-old female a case with avulsion of the left main bronchus occurring after blunt chest trauma due to a down fallen wall. A successful surgical repair of the totally avulsed left main bronchus was carried out. The post-operative course was uneventful with improvement in the respiratory status. The patient regained wellness within days in the in intensive care unit, and the diagnosis of traumatic rupture of the left main bronchus was approved by bonchoscopy and the computerized tomography (CT) scan of the chest. Surgical repair of the disrupted left main bronchus was accomplished 10 days from the admission and the bronchoscopic evaluation of the anastomosis and patency was achieved. The patient was discharged well with her lung fully expanded on chest X-ray. She is doing well during the follow-up period. The diagnosis and preoperative management of this uncommon post traumatic condition is discussed. We conclude that, in a patient with sustained severe blunt thoracic trauma, a high index of suspicion for trachea-bronchial disruptions must be maintained to detect these rare lesions. Skilful and early surgical treatments are required for proper management of such cases.

Key words: Bronchus, Avulsion, Blunt trauma

1. Introduction

Tracheobronchial injuries are rare and occur in less than 1% of patients following blunt chest trauma, the incidence is low, and most patients with this type of injury do not survive to reach hospital care (1, 2).Thoracic injuries are the second leading cause of death in paediatric blunt trauma. The evaluation of children with blunt thoracic trauma in the emergency department usually includes physical examination and plain chest radiography (3).

2. Case Presentation

A 14-year-old female was admitted to our hospital, three days following blunt chest trauma. She was crushed at the level of her chest between the fallen wall and the floor. Immediately following the accident, she was admitted to a remote hospital while she was conscious, but unstable hemodynamically with hypoxia and hypercapnia indicating respiratory distress. After the resuscitation, the chest radiograph showed opacity in the left hemithorax and mediastinal emphysema, but no pneumothorax. The diagnosis of a haemothorax was assumed, and a chest tube drain (CTD) was inserted. However, there was neither any blood drainage, nor any air leak through the CTD. She was referred to our department after three days of conservative management without any evidence of improvement, with persistent left chest pain and shortness of breath. Clinical examination of the chest showed bruising on the anterior chest wall and lower left neck with totally restricted left chest respiratory movements, and absent air entry on the left side accompanied by subcutaneous emphysema. Plain chest radiograph (Figure 1) revealed a left sided opaque hemithorax with mediastinal shift to the right, and right clavicular and left scapular fracture.

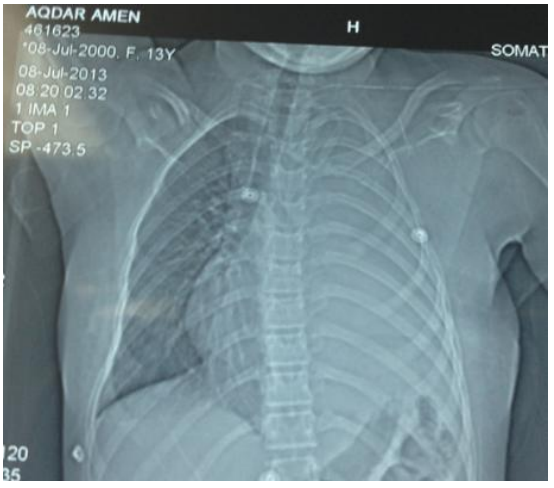

Figure 1. CXR showing mediastinal shift

The patient was ill, tachypneic and distressed. Thus, she was transferred to the intensive care unit in which the patient received oxygen by mask, antibiotics and analgesia. By the next day, she became better with normal O2 saturation on room air. Dynamic computerized tomography (CT) scan was performed for the patient on the third day which showed no evidence of vascular injury, but there was complete collapse of the left lung. Although the evidence of discontinuation of the left main bronchus was present, the avulsion of the LMB was not reported (Figure 2). Our decision was to consult the pulmonologist to perform a flexible bronchoscopy. On bronchoscopy, a serious amount of gray-blackish secretion was aspirated from the left main bronchus, the bronchus was totally obstructed and the suspicion of a complete disruption was confirmed. Unfortunately the instrumentation of the blind-ended left main bronchus, tension pneumothorax developed and the lung collapsed revealing an apparent fallen lung sign (Figure 3). Reinsertion of a CTD was carried out for decompression, which resulted with the in stabilization of the patient. However, there was neither any continuous air leak, nor an expansion of the lung.

Figure 2. Discontinuation of the left main bronchus with complete collapse of the left lung

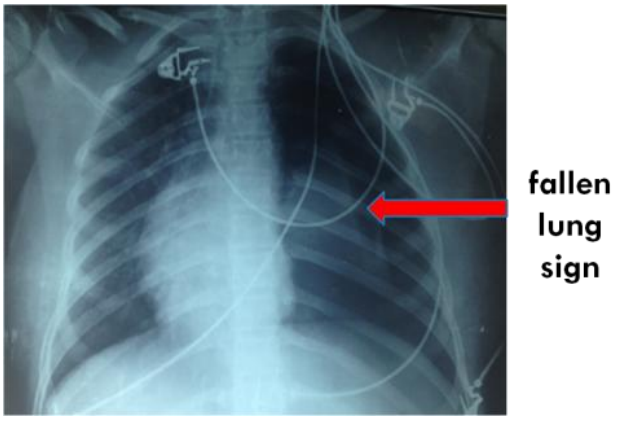

Figure 3. CXR after the diagnostic bronchoscopy

The decision of her family was to continue on conservative treatment and they postponed their consent for surgical intervention for few days during which the medical management was maintained including antibiotics, nebulizer bronchodilators, mucolytics, non-invasive continuous and intermittent positive airway pressure without clinical or radiological improvement.

Several days later, exploratory thoracotomy was performed. A double lumen endotracheal tube was inserted to ventilate the right lung. She underwent a left postero-lateral thoracotomy through the fifth intercostal space. After incision of the mediastinal pleura, meticulous dissection of the posterior and superior aspect of the hilum and the infero-medial aspect of the aortic arch to identify and mobilize the proximal and distal stumps was carried out. With the assistance of the anaesthesiologist by blowing the left lung, this manoeuvre confirmed complete separation of the left main bronchus at its distal part and the proximal stump displaced below the aorta and to the right side. After the identification of this injury, the dissection was continued to release and mobilize the both stumps of the left main bronchus in order to approximate both ends without tension (Figure 4).

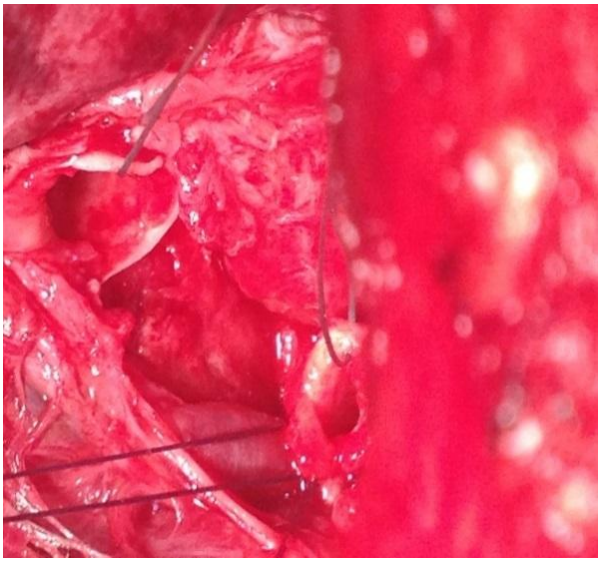

Figure 4. Surgical field showing interruption of the left main bronchus and both stumps marked with stay sutures

After mobilization of the transacted LMB, it was reconstructed primarily by end-to-end anastomosis with interrupted 2-0 polyglactin sutures. Blowing through the double lumen tube showing full expansion of the left lung (Figure 5), a watertight seal of the anastomosis was confirmed, and the pleura was closed over the anastomotic site. The CTD was secured in its place. Following haemostasis the thoracotomy wound was closed.

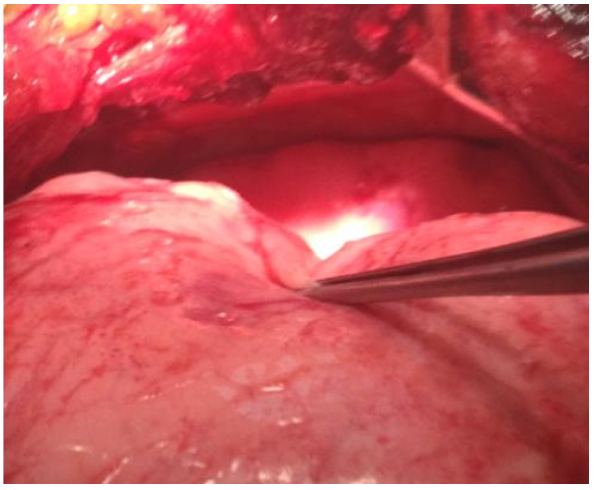

Figure 5. Surgical field after bronchial reconstruction with end-to-end anastomosis showing a fully expanded left lung

Immediate evaluations were made in the postoperative few hours. The clinical examination in the ICU confirmed good air entry and respiratory sounds. A chest X-Ray was done on the next postoperative day which showed left lung atelectasis. Thus, postoperative flexible bronchoscopy was necessary which revealed mucus plugs, retained secretions and debris obstructing the LMB which were removed by saline irrigation and suctioning. With use of bronchoscopy, the successful repair and patency of the airway was confirmed (Figure 6). Immediately, the O2 saturation was raised and the air entry and breath sounds were well auscultated. On the second postoperative day, there was dramatic clinical improvement and the X-ray revealed good lung inflation (Figure 7). The patient was transferred to the ward, and was discharged on the seventh postoperative day in normal pulmonary status, with an excellent general condition and the Chest x-ray revealed complete inflation of the left lung (Figure 8).

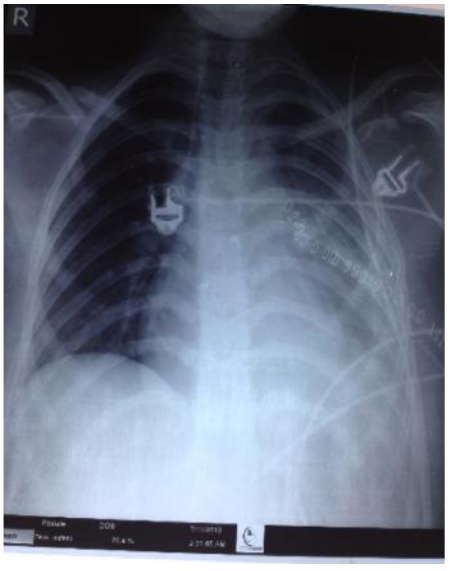

Figure 7. CXR on 2ndPOD showing a well expanded lung

Figure 8. CXR on the day of discharge showing a fully expanded left lung

3. Discussion

This is a report of a 14-year-old female patient who suffered from blunt chest trauma that needed management in an intensive care unit. Tracheobronchial injuries are associated with a high degree of lethality (3, 4) which is related to

significant thoracic compression injuries, including fractures to the ribs and clavicle, as well as cardiac and pulmonary contusions (5). The highest incidence of airway injury occurs at the sites of mediastinal attachment within 2.5 cm of the carina as result of shear develops between restrained and unrestrained airways by rapid deceleration, leading to disruption of the bronchus (5). The most common presenting signs of airway disruption include subcutaneous emphysema, dyspnea, sternal tenderness, and hemoptysis. Radiographic findings are most commonly pneumothorax, pneumomediastinum, and clavicle or rib fractures (4, 6). In our case, beyond the acute stage, the presenting symptoms were subtle also the patient did not show pneumothorax or air leak either clinically or radiologically to suggest the presence of tracheo-bronchial disruption which was contained by the mediastinal pleura. The left main bronchus rarely rupture into the pleural space in contrast to the right main bronchus which have the potential to rupture into the right pleural space with prolonged or high-pressure ventilation (5). Associated injury; intrathoracic or extrathoracic is an important mortality factor (4, 6). The predictors that can be used to create a sensible clinical decision rule for the identification of children sustaining blunt torso trauma include; low systolic blood pressure, elevated respiratory rate, abnormal results on clinical thoracic evaluation, femur fracture, and a GCS score of less than 15 (1). However, failure of the lung to expand in our patient aroused the suspicion of a bronchial injury and bronchoscopy confirmed it. Significant bronchial injuries may occur in the absence of usual initial symptoms. Therefore, the patients of obvious chest trauma should be on follow-up in the early post-injury period for detecting these lesions to avoid unnecessary morbidity and possible mortality (6, 7). CT and flexible bronchoscopy are the major tools necessary for early diagnosis and treatment (6, 8, 9).

Surgical reconstruction of the ruptured left main bronchus was accomplished ten days from the admission by end-to-end anastomosis of the transverse bronchial rupture. Other types of bronchial ruptures are longitudinal (10) or complex, consisting of rupture of the distal trachea and both main bronchi. Complex lesions are very rarely seen, comprising 8% of all ruptures, and the use of cardiopulmonary bypass increases the margin of safety during operation (6).

Successful repair was confirmed by bronchoscopy .The patient was discharged well with the lung fully expanded on the chest X-ray. She was instructed to keep in touch for the next bronchoscopy to check the anastomotic site, the presence of bronchial stenosis and a possible need for dilatation. The patient is still well during her follow-up period.

We conclude that, in a patient with sustained severe blunt thoracic trauma, a high index of suspicion for trachea-bronchial disruptions must be maintained to detect these rare lesions. Skillful and early surgical treatments are required for proper management of such cases.

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CASE REPORT

Cutaneous Schistosomiasis

Al-Samawi A. S.[1,*]

[1] *Department of Pathology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen*

[*] **Correspondence author:**
E-mail: abdullahalsamawi@yahoo.com

Abstract:

Cutaneous schistosomiasis is extremely rare even in endemic regions. I report a case of a 9-year-old girl had infected by schistosoma and presented late with vulval warty partly ulcerated nodule, the diagnosis was made on the basis of a routine skin biopsy by identification of schistosoma haematobium eggs deposited in the skin tissue and surrounded by inflammatory infiltrate with mild dysplastic change of epidermis. Dermatologists should be aware of this presentation of schistosomiasis when evaluating patients with unusual skin lesions.

1. Introduction

Schistosomiasis is a parasitic disease caused by several species of trematodes flatworms of the genus schistosoma. It is often endemic throughout wide area of the tropics and subtropics and produce chronic illness that can damage internal organs and, in children, impair growth and cognitive development. After malaria, schistosomiasis is the second most common health disease in Yemen (1). The cutaneous manifestations of schistosomiasis result from (a) penetration of the skin by the infective stage cercariae resulting in schistosomal dermatitis; (b) urticaria, oedema, fever, and pruritus which are hypersensitivity manifestations of invasion; and (c) ectopic deposition of ova in the skin tissue by adult worms which have passed in to the superficial veins and considered as very rare usually even in endemic regions (2).

2. Case Presentation

A 9-year-old girl presented with a 6 months history of burning micturation with persistent vulval ulcer without response to topical dermatological therapy. Physical examination disclosed a painless, warty partly ulcerated nodule on the left labia major (Figure 1). Microscopic urine and stool analysis were negative for schistosomal eggs. A punch biopsy specimen was obtained from the lesion and sent to the histopathologist where it was processed as for routine paraffin embedding. Sections were cut and stained by Hematoxylin and Eosin. Histological diagnosis of cutaneous schistosomiasis was made. Sections revealed a deposition of viable schistosomal eggs with terminal spine in the epidermis and dermis surrounded by inflammatory cells infiltrate mostly eosinophils. The epidermis shows acanthosis with mild dysplastic change (early intraepithelial neoplasia) in form of mild and hyperchromatic and pleomorphic nuclei of the lower third of epidermal thickness (Figure 2).

Figure 1. Perigenital warty partly ulcerated nodule on the left labia major (arrow)

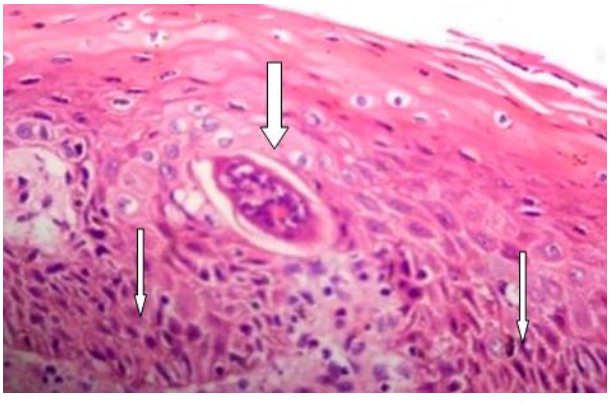

Figure 2. Histopathology of skin revealing deposition of a viable schistosoma egg with terminal spine (thick arrow). Note the epidermal acanthosis and lower third hyperchromatic and pleomorphic nuclei (thin arrows). (Hematoxylin and eosin stain x 400)

3. Discussion

Cutaneous schistosomiasis is extremely rare, even in endemic regions. It is usually leads to non-specific papulonodular lesions in the perigenital area (3). Whereas symptoms and signs of urinary and gastrointestinal forms of the infection are recognized readily, cutaneous manifestations produced by adult and eggs deposition are still a challenging of diagnosis (4). Cutaneous schistosomal manifestations occur with all three

subspecies of schistosoma. Skin involvement may occur at the site of penetration of the schistosomal cercariae released by snails in fresh water lakes and presents as an itching papular eruption occurring 1-2 h after exposure, lasting a maximum of one week and resolving spontaneously. An urticaria reaction can occur 4-8 weeks after exposure with an immune-complex mediated illness manifest as fever, purpura, arthralgia and abdominal pain, resolving spontaneously within 4-6 weeks. The cercariae pass via the lungs and liver into the portal venous system and adult flukes lodge in the venous plexuses. Direct retrograde spread of the adult flukes from their usual sites into the venous system supplying vulval skin leads to deposition of ova in the skin and subsequent formation of genital granulomas, as in our patient. The skin lesions are most frequently found in the perigenital area of female patients. Extragenital skin lesions are seen less frequently (5). The diagnosis of ectopic schistosomiasis cannot be depending on the bases of standard urine analysis. Hence the diagnosis is based on the demonstration of schistosoma hematobium eggs in examined tissue (6). The lesion responds to conventional therapy and resolve within 5 months (7). In the presenting case, the epidermis shows mild dysplasia (early vulval intraepithelial neoplasia), unusual association between vulval schistosomiasis, microinvasive squamous cell carcinoma of vulva and high-grade vulval intra-epithelial neoplasia in a human immunodeficiency virus-positive patient was reported previously (8). Cervical schistosomiasis seems to be a possible risk factor for the development of cervical intraepithelial neoplasm and cancer (9). Schistosoma haematobium alone is not the causative agent for the abnormal proliferation of squamous epithelium of the cervix as well as vulva; it acts as a cofactor by traumatizing the genital epithelium or immune suppression to favour human papilloma virus infection (10). However, early mild change in the epidermis of our patient may be due to short duration of disease and early diagnosis. Dermatologists should be aware of this presentation of schistosomiasis when evaluating patients with unusual skin lesions.

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