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RESEARCH ARTICLE

AUTOPSY STUDY OF ADRENALS - A PROSPECTIVE STUDY

***,[1]Dr. Trupti Dongre and [2]Dr. Urmi Chakravarty Vartak**

[1]Department of Pathology, NKP Salve Institute of Medical Sciences and Research Institute, Hingna, Nagpur, India

[2]Department of Pathology, Lokmanya Tilak Muncipal Medical College and Lokmanya Tilak Muncipal General Hospital, Sion, Mumbai, India

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ABSTRACT

Background: Adrenal glands are the least studied organ.
Aim and objective: To study the gross and histomorphological changes of adrenals in various stress related conditions including mainly the non-neoplastic conditions and patients dying due to any kind of shock. Also to study the co-relation of changes in adrenals with the clinical presentation of the patient.
Material and method: Retrospective and prospective study of one hundred and eight cases in a tertiary care hospital in a period between May 2007 to Nov 2009.
Results: Out of 108 cases, various adrenal lesions were found in 93 cases while only 15 cases had normal adrenals.
Conclusion: Adrenal lesions can present in various forms at autopsy. Non-neoplastic lesions should be given equal importance as neoplastic. An enlarged adrenal does not always indicate malignancy. There are many clinical conditions in which adrenals are affected as secondary phenomenon. Gross and histomorphological examination of the tissue can diagnose the adrenal lesions with great accuracy and is beneficial for patients further survival, in setups where facilities to perform adrenal biopsies is available. Adrenals should be investigated as a part of routine autopsy procedure in all postmortem cases.

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INTRODUCTION

The adrenal glands in human are paired endocrine organs, composed of cortex and medulla, which have distinctly different embryogenesis, structure and function. As correctly adrenals are called as ''stress-glands''. Adrenal glands are involved in each and every stress related condition, including both neoplastic and non-neoplastic conditions. These glands secrete variety of hormones to control the stress. With the advent of advanced radiological techniques, more and more of lesions are picked up. With increased number of C T guided biopsies, the pathologists are challenged to give the diagnosis on a small amount of tissue. The clinical spectrum of these conditions is varied. Some of the patients present with excess hormone secretion and others with adrenal insufficiency, but a large number of the patients are asymptomatic.

Corresponding author: Dr. Trupti Dongre
Department of Pathology, NKP Salve Institute of Medical Sciences and Research Institute, Hingna, Nagpur, India

It is therefore very essential for the pathologists to know the histomorphological spectrum of the changes in adrenals in various types of conditions. Hence, we studied the gross and microscopic morphology of adrenals in various types of "stress–related conditions" and their clinicopathological co-relation. Light microscopy can diagnose the majority of conditions with good reliability. Laboratory and clinical data along with spectrum of stains and ancillary techniques also supplement correct diagnosis.

MATERIALS AND METHODS

An analysis of adrenal lesions was done in the department of pathology at a tertiary care referral hospital. The study included 108 cases of acute shock and chronic stress, from May 2007 to Nov 2009. Autopsy records were scrutinized and details of the age, sex, clinical presentation, autopsy findings were obtained. Further the final cause of death was also recorded and related findings in other organs were also noted.

On gross examination, the dimensions, laterality, colour, nodularity, atrophy, hypertrophy were noted. If a tumor was present- its size, encapsulation, colour, site, appearance, edge, cut surface were noted. Hemorrhage and if any cyst present, were also noted. The slides of all cases were stained with hematoxylin and eosin. The Hematoxylin and eosin stained slides were evaluated. Special stains and ancillary techniques were used wherever necessary.

RESULTS

Table 1. Total number of autopsies

Total autopsies	108
Adrenal lesions	93
Normal	15

Table 2. Age-wise Distribution of Autopsy findings

Age (Yrs)	Normal	Adrenalitis	Congestion	Nodules	Loss of Lipid	Hemorrhage	Necrosis	Pigment	Metastases	Atrophy	Hypertrophy
15-25	3	10	10	1	3	6	3	-	-	-	-
26-35	1	6	7	6	2	6	8	1	1	-	1
36-45	6	7	5	8	5	1	1	2	1	-	1
46-55	2	9	6	4	2	3	1	1	-	-	-
56-65	2	7	6	4	5	3	1	-	2	1	-
66-75	1	-	5	2	3	-	-	-	-	2	-
76-85	-	2	1	1	-	1	-	1	-	-	-
86-95	-	-	-	-	1	-	-	-	-	-	-
Total	15	41	40	26	21	20	14	5	4	3	2

Table 3. Male and female ratio

Sex	Percentage
Male	60.22%
Female	39.78%

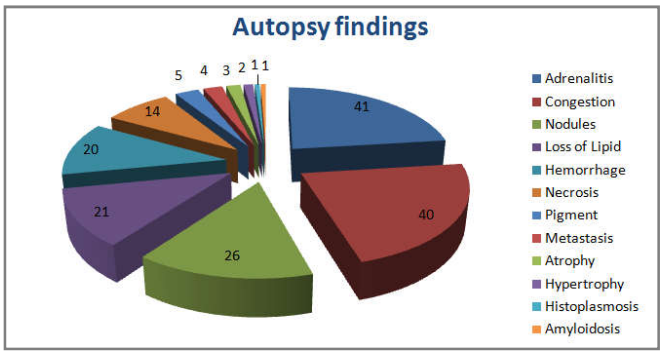

Figure 1. Distribution of adrenal lesions

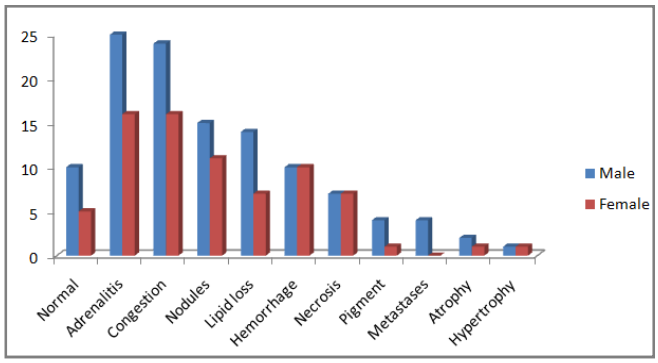

Figure 2. Sex ratio in various adrenal lesions

Table 4. Hemorrhage

Sr .No	Cause of Death	No. of cases
1	IPH	7
2	Septicemia	5
3	Hypovolumic shock	3
4	TB Bronchopneumonia	2
5	Pneumonia	2
6	Adrenal Hemorrhage	1
7	Raised ICT	1

Table 5. Adrenalitis

Sr. No.	Cause of Death	No.of cases
1	IPH	12
2	Septicemia	8
3	Hypovolumic Shock	8
4	Cardiac Failure	4
5	Raised ICT	3
6	TB	3
7	Others (RF/PE)	3

Table 6. Nodules

Sr.No.	Cause of Death	No. of Cases
1	Septicemia	8
2	Cardiac failure	7
3	Pneumonia /TB Bronchopneumonia	4
4	Renal failure	3
5	Hypovolumic shock	2
6	Raised ICT	2

Table 7. Loss of Lipid

Sr.No	Cause of Death	No. of Cases
1	Septicemia	9
2	Cardiac	5
3	Raised ICT	2
4	Lung Cancer	1
5	Hypovolumic shock	1
6	Encephalopathy	1
7	Pulmonary edema	1
8	IPH	1

Table 8. Necrosis

Sr No	Cause of death	No of cases
1	Hypovolumic shock	3
2	Cardiac failure	3
3	Septicemia	2
4	IPH	2
5	Tuberculosis	2
6	Raised ICT	1

Table 9. Pigment

Sr.No	Cause of death	No. of cases
1	IPH(AFI)	3
2	TB(AFI)	1
3	Bronchopneumonia	1

DISCUSSION

Involvement of adrenal glands by neoplastic conditions are relatively rare, but the non-neoplastic conditions are quite common. Same was observed in our study. In our autopsy study of adrenals in 108 cases, 86.11% cases showed

pathological changes, with only 13.89 % appearing normal (Table 1). For understanding of the pathophysiology and its association with the clinical presentations, adrenal lesions are classified into various types. In our study there is predominance of non-neoplastic 96.3% adrenal lesions with neoplastic conditions comprising 3.7 %. The non-neoplastic lesions comprised of adrenal inflammation (adrenalitis) 37.96 %, hemorrhage 18.52 %, nodules 24.07%, loss of lipid 19.44 %, necrosis12.96 %, pigment 4.63%, congestion 37.04 %, atrophy 2.78 %, hypertrophy 1.85 %, metastasis 3.7% (Fig. 1).

Table 10. Congestion

S.No	Cause of death	No of cases
1	Septicemia	10
2	IPH	10
3	Hypovolumic shock	8
4	Cardiac failure	4
5	Raised ICT	3
6	TB Bronchopneumonia	3
7	Cachexia (Malignancy)	1
8	Lobar pneumonia	1

We had a single case of histoplasmosis and amyloidosis. The majority of adrenal lesions were seen in the age group of 3 rd to 6th decade, i.e., 97.22 %. The least number of cases were seen in elderly age group 2.78 % (Table 2). In our study there was male dominance (60.22 %), over females (39.78 %) (Table 3) (Fig 2). All the metastatic tumors were seen in males. In our study the lesions predominantly occurred bilaterally , including adrenalitis, hemorrhage, nodules, loss of lipid, necrosis, pigment, hypertrophy, atrophy, histoplasmosis, amyloidosis. Unilateral involvement was seen in 3 cases of metastasis.

Adrenal hemorrhage (Table 4)

Adrenal hemorrhage has been reported in 0.14% to 1.1% of autopsied patients (Xarli *et al*., 1978) (Fig 4). It can show unilateral or bilateral involvement. There were 20 cases, 18.52 % of hemorrhage in our study. All cases, showed bilateral involvement. It can occur in any age from neonate to elderly patients (Khuri *et al*., 1980). Our study included age group of 15 years to 95 years old. The causes of hemorrhage can vary from sepsis, acute febrile illness, shock and even spontaneous hemorrhage. In a review of 22 cases of hemorrhage, Vasiki et al. reported various causes like septicemia 41%, anticoagulant drugs 23%, spontaneous 18 % (Xarli *et al*., 1978). The most common cause of hemorrhage in our study was intrapulmonary hemorrhage (35%) due to acute febrile illness. The second most common cause was sepsis (25%). Other causes were hypovolumic shock, bronchopneumonia and raised intracranial tension.

There was a single case of spontaneous hemorrhage. Salkade *et al.* studied 62 cases of leptospirosis, showed hemorrhages in multiple organs including adrenals (Salkade *et al*., 2005). Various concomitant diseases have been reported by Vasiki *et al.* such as hepatic necrosis, septicemia, alcoholism, pregnancy (Xarli *et al*., 1978), which were also observed in our study. The adrenal insufficiency due to bilateral adrenal hemorrhage develops rarely but can be life threatening. There was a single case of spontaneous adrenal hemorrhage of a 27 year male, presenting with fever, loose motions and pain in abdomen, duration of his stay in the ward was only 50 minutes. The patient died due to adrenal insufficiency.

Adrenalitis (Table 5)

Inflammation of the adrenals may result from an autoimmune mechanism, infection or a variety of other causes. Autoimmunity is caused due to autoantibody reactivity against the adrenal cytochrome P450 enzymes (Weetman, 1995). In our study, total 41cases of adrenalitis were seen. The most common cause for adrenalitis in our study was infection, due to febrile illness 29.27% resulting in intrapulmonary hemorrhage, septicemia 19.51%, and hypovolumic shock 19.51%. Out of the total cases, two cases shows features of extensive adrenalitis: 55 years male, duration of stay in ward 13.5 hrs, presented with complaints of high grade fever with chills, vomiting, loose motions, giddiness. His creatinine was 3.4mg/dl. Other additional feature seen in adrenal was congestion. The cause of death of the patient was shock following acute gastroenteritis. 58 years old male, duration of stay in ward was 8 hrs, presented with complaints of fever with chills, breathlessness, loose motions. Chest X-ray showed bilateral lower zone infiltrates. Other additional feature seen in adrenal was foci of hemorrhage. The cause of death of the patient was intrapulmonary hemorrhage in case of acute febrile illness.

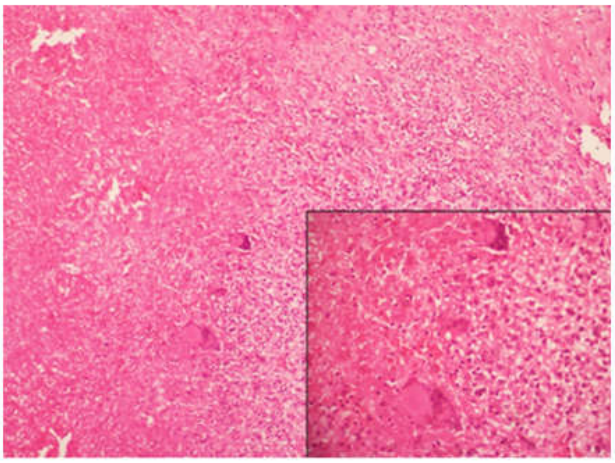

Fig. 3. Section of the adrenal showing large area of caseous necrosis with langhan's giant cell formation [100X]. (Inset) [H and E, x 400]

All the layers of the cortex are involved in adrenalitis, but the medulla is unaffected. A single case of focal lymphoid aggregate in the medulla was present, the patient was a 50 year male, chronic alcoholic presented with complaints of breathlessness, cough, fever and abdominal distention. Clinical examination showed presence of icterus. His clinical diagnosis was pulmonary edema with alcoholic liver disease. Focal aggregates of lymphocytes are a normal finding with increasing frequency in the adrenal gland of the older patients (Hayashi *et al*., 1998), which were not included.

Adrenal nodules (Table 6)

Dobbie *et al.* reported that incidental cortical nodules can be seen every region of the cortex and some of them can reach size as high as 2 to 3 cms (Dobbie, 1969). The incidence of

unsuspected adrenal masses varies from 0.6 to 1.3%. They are more common in hypertensives and diabetics (Glazer *et al*., 1982). In our study total 26 cases (24.07%) show nodules in adrenals, with the most common age group of 26 to 65 years of age and the most common clinical diagnosis was septicemia 30.77% followed by cardiac failure 17.07% (Fig. 5). Out of 26 cases 6 cases (23.08%) were having history of diabetes and 6 cases (23.08%) were having history of hypertension, with 3 cases (11.54%) having both diabetes and hypertension. Shamma *et al.* shows autopsy report of adrenal cortical adenomas, 1.5 cms or more in diameter in as many as 20 % of hypertensive individuals at autopsy, but only 1.8 % of normotensive individuals (Russi *et al*., 1945). Spain *et al* and Hedeland *et al.* suggested the higher incidence of cortical nodules or nodularity increases with age and is associated with hypertension and in some cases diabetes mellitus (Shamma *et al*., 1958; Spain and Weinsaft, 1964).

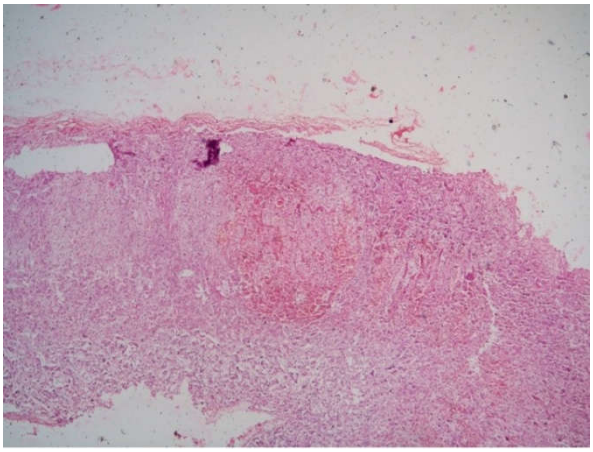

Fig. 4. Section of the adrenal showing cortical hemorrhage [H and E, x400]

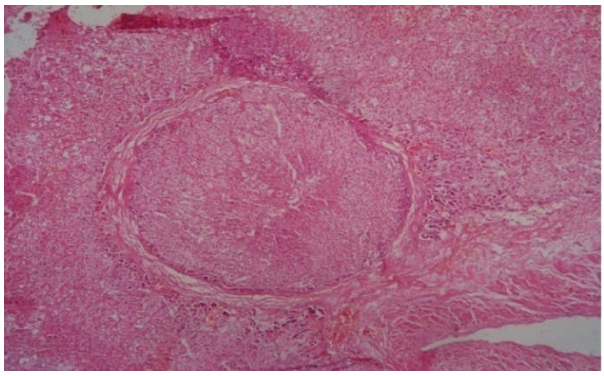

Fig. 5. Section of the adrenal showing cortical nodule near the central vein [H and E, x100]

Loss of lipid (Table 7)

Adrenals are affected by prolonged stress. This co-relates with stress related lipid depletion mediated by increased secretion of adrenocorticotropic hormones (Hedeland *et al*., 1968). Our study includes total 21cases (19.44%), showing lipid depletion, mainly in the zona fasciculata of the cortex and the cortico-medullary junction. The most common age group affected is 36years to 65 years. The commonest cause resulting in prolonged stress is septicemia 42.86%, followed by cardiac disease 23.81%. Symington T: conclude that vast majority of adrenal gland at autopsy shows some changes of lipid depletion and it is rare to find ‘’normal’’ adrenal gland at autopsy (Stenberg’s, Fifth edition). In a study of Glasgow *et al*, patients died of AIDS, the adrenal gland shows lipid depletion. Of the 41 patients in their study, focal lipid depletion occurred in 25 cases, diffuse depletion in 16 and a pattern of lipid reversion was seen in 3 cases with focal depletion (Syminton, 1969; Glasgow *et al*., 1985).

Adrenal necrosis (Table 8)

Adrenal necrosis can follow various infective etiology. Our study includes total 12 cases (12.96%) cases of adrenal necrosis. The necrosis is mainly localized at the cortico-medullary junction. Most common age group involved ranges from 15 years to 35 years. The most common cause of death in these patients was hypovolumic and cardiogenic shock equally (21.43%), followed by sepsis, intrapulmonary hemorrhage and tuberculosis, with only one case of raised intracranial tension.

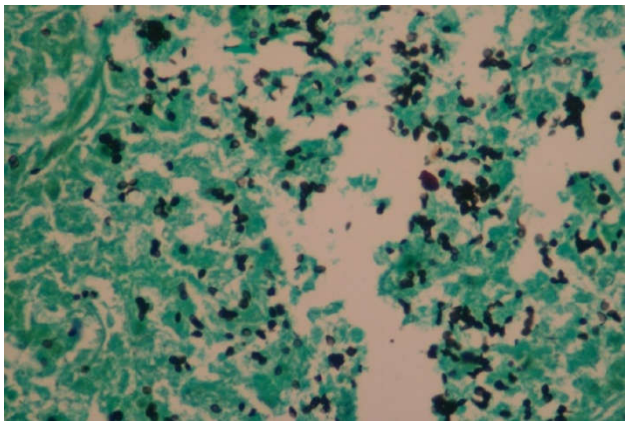

Fig.6 a. Close view of the cut surface of the adrenal showing necrosis in Histoplasmosis

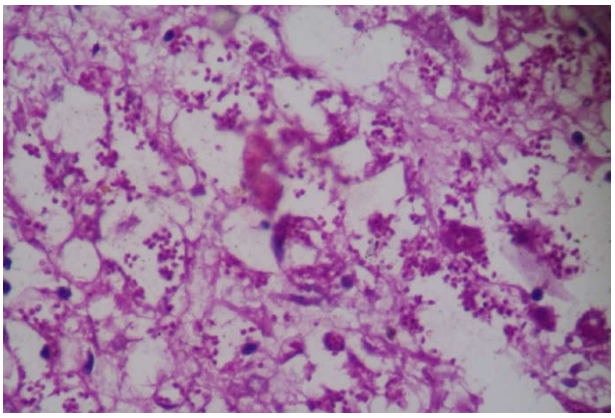

Fig. 6b. Section of the adrenal showing black colored fungal organisms of Histoplasmosis [GMS, x400].

Adrenal necrosis due to tuberculosis

Out of the total 8 cases of tuberculosis in our study, only 3 cases showed necrosis and from which only 2 cases showed extensive areas of caseous necrosis with Langhan’s giant cell formation (Fig. 3). Both these case showed features of adrenal insuffiency due to tuberculosis. Out of the 2 cases, the first case was of 28 year male, who presented with respiratory symptoms

of cough and dyspnea with fever. The second case was of a 26 year six months gravid female. She presented with complaints of dry cough, fever with chills and vomiting. Both of these patients died due disseminated tuberculosis. Although in India tuberculosis is the most common cause of Addison's disease (47%) due to bilateral destruction of both the glands (Ernest E.Lack, First edition). The classic granulomatous reaction with abundant epitheloid histiocytes may not be seen in adrenals because of local high titers of steroid often blunt the host inflammatory response (Abecassis *et al*., 1985). In India adrenals are affected frequently as a part of miliary dissemination and this is usually seen at the autopsy (Abecassis *et al*., 1985). Out of the 3 cases, 2 cases show disseminated involvement of adrenals with lungs and other organs (liver, spleen, kidney). The remaining case was of tuberculous bronchopneumonia.

Adrenal Metastasis

Autopsy studies have revealed adrenal metastasis in 9 to 27 percent of cancer patients (Agarwal *et al*., 2001). Our study had 4 cases (3.7 %), of adrenal metastasis all of which were autopsy cases. Various studies have indicated the most common age of metastatic adrenal tumor to be in the 5 to 7 th decade. Our study showed 50% occurring in the age of 5 to 7th decade. In our study all of the metastasis are caused due to primary in the lungs, and all of our patients affected are males. The other most common primary sites for metastatic adrenal tumor are breast (12.58%), lung (28.42%), melanomas (40%), gastric cancers (16%), colorectal (14%). Although metastasis to adrenal gland is relatively common, clinical adrenal insufficiency due to metastatic carcinoma is very rare (Glomset, 1938). The diagnosis of adrenal insufficiency due to metastatic carcinoma may be underestimated since the relatively nonspecific symptoms of Addison's disease may be mistaken for cachexia of malignancy. This is supported by reports of adrenal insufficiency in patients with known metastatic cancer and C T evidence of bilateral adrenal enlargement in 19 percent to 33 percent of cases. These observation suggest that endocrinologic testing for adrenal hypofunction should be performed in all patients with metastatic carcinoma who are found to have bilateral adrenal enlargement on C T scan, in addition, cancer patients who develop symptoms of adrenal in suffiency should have CT scans of the adrenals. If adrenal enlargement is found, CT guided biopsy is useful in investigating metastatic malignancy. Hormonal replacement may result in palliation of symptoms and prevention of death from Addison's disease (Glomset, 1938).

Adrenal amyloidosis

Browning *et al.* in his study of 124 patients with amyloidosis found out that adrenal amyloidosis was very rare and mostly secondary in nature (Redman *et al*., 1987). We had one case of amyloidosis in our study, which was detected incidentally at autopsy as a part of systemic amyloidosis (Fig. 7). A 42 year old male, hypothyroid, presented with diarrhea, oliguria, anorexia. The adrenals were enlarged and other organs affected were kidney, spleen, and pancreas. Special stain for Congo red was positive. The patient died due to congestive cardiac and renal failure. Danby *et al.* studied adrenal status of 22 patients with renal amyloidosis. Amyloid deposition was found in the adrenal glands in seven patients who died of systemic amyloidosis and renal failure (Browning *et al*., 1985). Of these 4 patients died of addisonian crisis and hypoadrenalism probably contributed to the death of further 2 patients.

Adrenal Histoplasmosis

Goodwin *et al* reviewed 102 cases of disseminated histoplasmosis and found that adrenal was involved in 82% of the cases (Danby *et al*., 1990). Histoplasma can also produce bilateral enlargement of the adrenal gland. Our case is of a 57year male, who presented with pain in abdomen and dyspnea. He was in a gasping state and the duration of stay was only 55mins.The patient was cachexic. On autopsy we found bilaterally enlarged adrenal glands measuring 6 X 5 X 2cms; with areas of necrosis (Fig. 6). Histology revealed granulomatous inflammation with areas of necrosis and macrophages with several basophilic organisms having halo around them. Special stains for fungus, later proved the organism to be histoplasma (Fig. 6 a) (Fig. 6 b).

Fig. 6. Section of the adrenal showing fungal organisms of Histoplasmosis [PAS, x400]

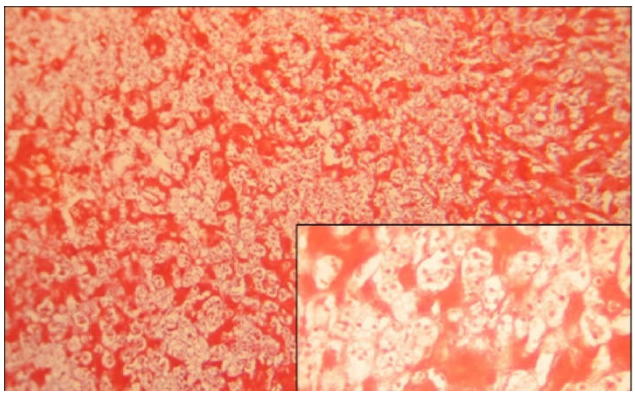

Fig. 7. Section of the adrenal showing Congo red (positive) stain of amyloid [Congo redx100]. (Inset) [Congo redx400]

Pigments (Table 9)

In our study we found 5 cases (4.63%), which showed brown-black pigment deposition in the adrenals. The most common age group is 26 to 55 years. The most common cause of death of these patients was intrapulmonary hemorrhage (three cases) 60% due to acute febrile illness. The rest of the two cases, one had tuberculosis with acute febrile illness and the other had bronchopneumonia.

Atrophy

Atrophy of the adrenal gland may be found in association with lesions primarily affecting the adenophysis or hypothalamus, leading to diminished secretion of ACTH (Goodwin *et al*., 1980). The administration of exogenous corticosteroids will produce similar changes as a result of suppression of ACTH. The adrenal glands in secondary hypofunctional states are considerably smaller than normal and the overall configuration is maintained (Stenberg's Diagnostic surgical pathology fifth edition). In our study we found 3 cases (2.78%) of adrenal atrophy. All of them lies in the age group of 56 to 75 years. And the common cause of death in all of them was cardiac failure.

Hypertrophy

Primary hyperaldosteronism is characterized by excessive secretion of aldosterone from the adrenal glands and is associated with suppression of plasma renin activity with resultant hypokalemia and hypertension (Stenberg's Diagnostic surgical pathology fifth edition), it is most often associated with or without formation of micro nodules (Ernest E. Lack, First edition). In our study we had 2 cases (1.85%), one patient was 45year male with hypertension. In these patients on histological examination there was thickening of zona glomerulosa. On investigating he was found to have hypokalemia (Stenberg's Diagnostic surgical pathology fifth edition). Another patient was a 29 year postpartum female with interstitial pneumonia. Both these patients showed formation of micronodules in addition to hypertrophy, secondary to hypertension (Stenberg's Diagnostic surgical pathology fifth edition). Isolated single case of 29 years postpartum female, presented with sudden onset breathlessness showed histological changes of tubular change formation in the cell cord of adrenal cortex of the adrenals (Rich, 1944). Another single case of a 46 year male, presenting with abdominal pain and breathlessness showed features of fibrosis in the histopathology of adrenals involving zona fasciculata and cortico-medullary junction. The patient died due to hemorrhagic pancreatitis.

Conclusion

Adrenal lesion can present in various forms at autopsy. Non-neoplastic lesions should be given equal importance as neoplastic. An enlarged adrenal does not always indicate malignancy. There are many clinical conditions in which adrenals are affected as secondary phenomenon. Gross and histomorphological examination of the tissue can diagnose the adrenal lesions with great accuracy and is beneficial for patients further survival, in setups where facilities to perform adrenal biopsies is available. Adrenals should be investigated as a part of routine autopsy procedure in all postmortem cases.

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