

Case Presentation

ASYMPTOMATIC PHEOCHROMOCYTOMA ASSOCIATED WITH VON RECKLINGHAUSEN'S DISEASE (NEUROFIBROMATOSIS TYPE1): CASE REPORT

AL GHAMDI, H., WAGIH , S., ASHOUR W. and DEWIK, Z. *

King Abdel Aziz Hospital & Oncology center, Jeddah- Al Taiif , KSA*

We report a case of 50 years old male with neurofibromatosis complaining of recurrent attacks of right loin pain. Clinically , the patient was normotensive , his body was full of neurofibromas with cafe au lait patches (Fig. 1, 2 & 3). Catecholamine in urine was markedly elevated. No other endocrinological abnormality depicted. CT scan abdomen revealed presence of right adrenal mass 5.9X5.9 cm with central necrosis and haemorrhage (Fig. 4 & 5). I 131 metaiodobenzylguanidine (I 131-MIBG) revealed a well defined sizable area of intense tracer accumulation at right suprarenal gland (fig. 6 & 7). The patient was operated upon and the histopathology proved to be benign pheochromocytoma.



Fig. (1): Multiple skin neurofibromas.



Fig. (2): Multiple skin neurofibromas & café au lait spots.

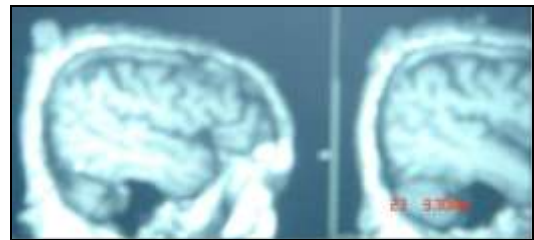


Fig. (3): MRI skull with multiple scalp neurofibromas.

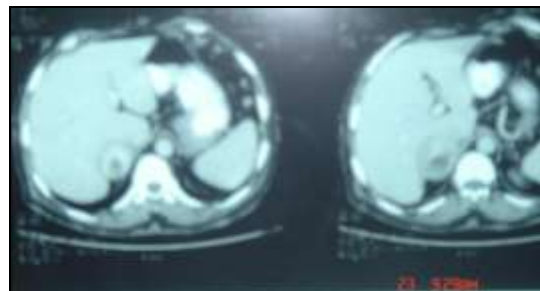


Fig. (4): CT scan showing sizable right suprarenal mass.

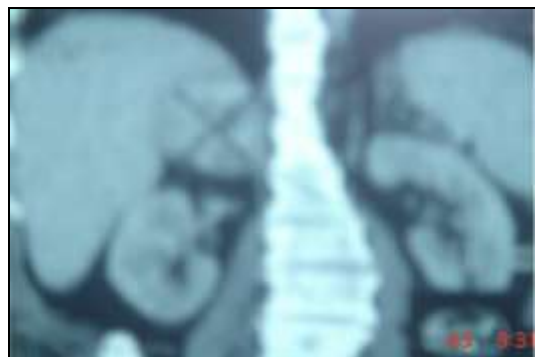


Fig. (5): CT scan with a sizable right suprarenal mass.

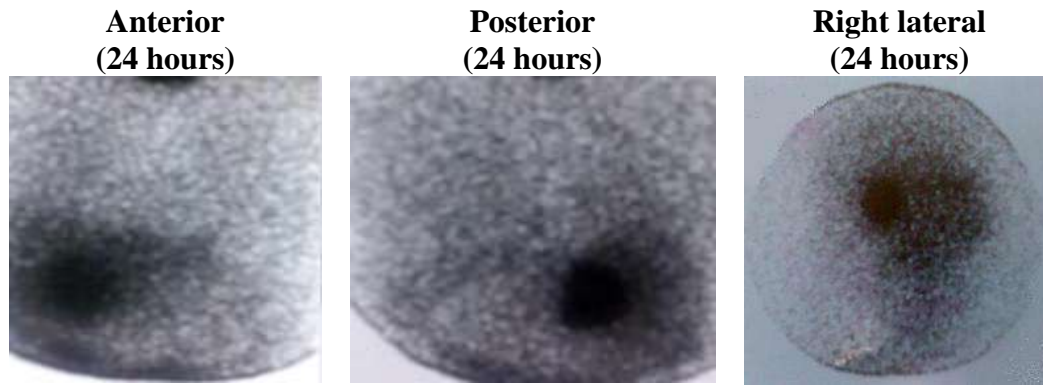


Fig. (6): 24 hours MIBG images with MIBG avid Rt. Suprarenal mass.

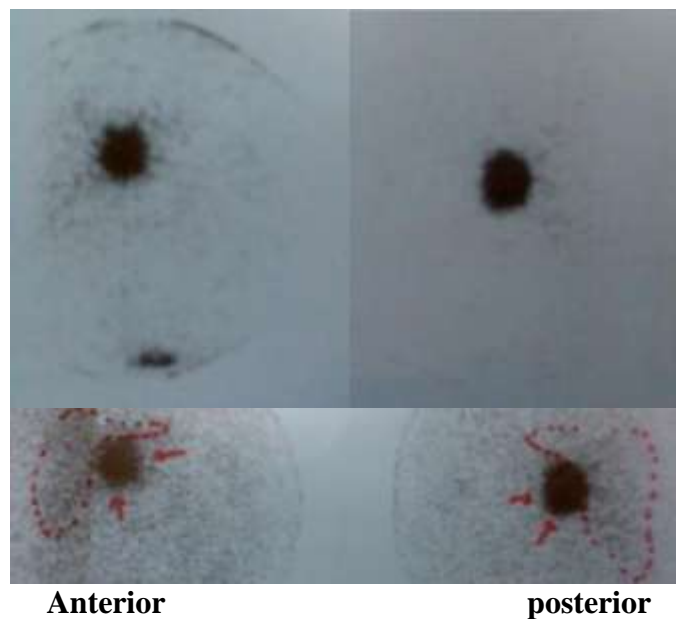


Fig. (7): 72 hours MIBG images with intense tracer uptake in right suprarenal mass.

DISCUSSION

Pheochromocytoma is a tumor of the adrenal medulla, which is benign in around 90% of patients. Although pheochromocytoma is rare, it is considered a major cause of correctable hypertension with a prevalence of 0.1-0.5% in hypertensive population (1). Hypertension is present in more than 90% of patients with pheochromocytoma presenting with clinical symptoms of paroxysmal attacks of headache, sweating, palpitation, stress and sense of imminent death. 9.5% of patients are

normotensive and 4.3% are asymptomatic and discovered accidentally (2). The non hypertensive course, as reported in our patient, is thought to be attributed to reduced vascular response to noradrenaline (3). Despite the fact that underlying genetic mechanisms of pheochromocytoma have been well investigated, they are still incompletely understood. In approximately 80% of patients tumor occur sporadically, in the remaining 20% it may occur with type II multiple endocrine neoplasia, type 1 neurofibromatosis or with von hippel

lindau disease (1). **Gosset et al., 1999** (4) pathologically compared 64 genetically determined pheochromocytomas (49 MENIIa, 3 MEN II b, 6 Von Recklinghausen's disease, 1 Von Hippel-Lindau disease and 5 familial pheochromocytomas), those with Von Recklinghausen's disease represent 10.7% of the whole genetically determined pheochromocytomas, with 48 sporadic tumors.

They reported that genetically determined pheochromocytomas are more observed among men and more frequently bilateral and multicentric than sporadic lesions. Also, genetically determined tumors were more differentiated with insular pattern, with less adrenal capsular invasion less necrosis and pseudocysts.

Neurofibromatoses are autosomal dominant diseases that have widespread effects on ectodermal and mesodermal tissue. It is classified into two distinct types, neurofibromatosis type1(NF1) and neurofibromatosis type2(NF2). The commonest member of the group is neurofibromatosis type1 (NF1), also known as von Recklinghausen disease. It occurs in about 1 in 3000 births, whilst NF2 only occurs in about 1 in 50000 births. They occur as a result of a defect in different genes. NF1 is caused by a mutation on a gene located on chromosome 17 and NF2 is caused by a mutation on chromosome 22. People with neurofibromatosis type 1 are born with one mutated copy of the NF1 gene in each cell. In about one half of the cases, the altered gene is inherited from an affected parent. The remaining cases result from new mutations in the NF1 gene and occur in people with no history of the disorder in their family. Unlike most other autosomal dominant conditions, in which one altered copy of a gene in each cell is sufficient to cause the disorder, two copies of the NF1 gene must be altered to trigger tumor

formation in NF1. Mutation of the second copy of the NF1 gene occur during a person's lifetime in specialized cells surrounding nerves. Almost everyone who is born with one NF1 mutation acquires a second mutation in many cells and develops the tumors characteristic of NF1(5).

Mutations in the NF1 gene cause neurofibromatosis type1, actually this gene provides instructions for making a protein called neurofibromin. This protein is produced in many cells, including nerve cells and specialized cells surrounding nerves (oligodendrocytes and schwann cells). Neurofibromin acts as a tumor suppressor, which means that it keeps cells from growing and dividing too rapidly or in an uncontrolled way. Mutation in the NF1 gene leads to the production of a nonfunctional version of neurofibromin that can not regulate cell growth and division, as a result, tumors such as neurofibromas can form along nerves throughout the body (6).

Neurofibromatosis type1 varies in severity and can affect all physiological systems. Most adults with NF1 develop neurofibromas which are the characteristic lesions of the condition and may be also found in the oropharynx and larynx (7). Neurofibromas are noncancerous(benign) tumors that are usually located on or just under the skin, these tumors may also occur in nerves near the spinal cord or along nerves elsewhere in the body. Besides, benign growths called Lisch nodules (tiny tumors on the iris) often appear in the colored part of the eye (the iris), these do not interfere with vision. Additional symptoms and signs of NF1 include skin folds frecklings, café au lait patches, high blood pressure, short stature, an unusually large head (macrocephaly), and skeletal abnormalities such as abnormal curvature of the spine (scoliosis). Although most people with

neurofibromatosis type 1 have normal intelligence, learning disabilities and attention deficit hyperactivity disorder (ADHA) occur frequently in affected individuals (7, 8, 9).

The association between Von Recklinghausen's disease and pheochromocytoma was reported to occur in 10% of patients (10). **Ventura et al. 1989** (11) stated that different kinds of neoplasia may be associated with neurofibromatosis with excessive frequency, and benign pheochromocytoma coexists in 10% of patients, yet, description of coexistence as a malignant tumor is a rarity. On the other hand **Landsberg and Young, 1992** (2), stated that 5% of patients with pheochromocytoma has neurofibromatosis and in patients with neurofibromatosis in one large series pheochromocytoma was present in < 1% of patients.

Walther et al., 1999 (12), reviewed 118 literature that characterize the clinical findings of Von Recklinghausen disease associated with pheochromocytoma from the years of 1966 to 1999, they reported that pheochromocytoma has been clinically identified in 0.1 to 5.7% of patients with Von Recklinghausen's disease. Mean patient age was 42 years with a range of 1.5 to 74 years, in 87 women and 61 men at presentation with pheochromocytoma. Out of the 148 patients, 84% had solitary adrenal tumor, 9.6% had bilateral adrenal tumor and the remaining 6.4% had ectopic pheochromocytoma. Symptoms related to pheochromocytoma or hypertension were noted in 78% of patients and the remaining 22% are normotensive and discovered accidentally. 87% of patients demonstrated I 131- MIBG uptake. They reported that pheochromocytomas occur in small but defined number of patients with Von Recklinghausen's disease and can be associated with significant

morbidly and mortality if not detected. They concluded that screening of patients with Von Recklinghausen disease seems to be indicated (10). This conclusion is consistent with what was previously reported by **Zoller et al., 1997** (13), who reviewed the follow up of 70 patients with NF1 in the period from 1978 to 1989, they found that 24% of them had malignant tumors. While benign tumors occurred in 10 patients, benign pheochromocytoma was found in 4 patients (6%). They stated that malignant tumors were more often in the NF1 patients than was expected in the general population matched for age, gender and time of follow up. They concluded that the development of tumors is part of the NF1 disease process, and this deserves attention both in the clinical setting and in family counseling dealing with complications of NF1 in adulthood (13).

REFERENCES

1. Opocher G., Schiavi F, Conton P, Scaroni C, and Mantero F: Clinical and genetic aspects of pheochromocytoma, *Horm. Research* ;59 suppl1:56-61, 2003.
2. Lewis Landsberg and James B Young: Catecholamines and the adrenal medulla, chapter 10 p; 621 - 705. In William's textbook of endocrinology, eds: Jean D William and David W Foster, Eighth edition Saunders company, 1992.
3. Matura K, Sonoda Y, Saigo R, Yoshioka T and Fukunaga H: A patient with von Recklinghausen's disease associated with polymyositis, asymptomatic pheochromocytoma, and primary hepatic leiomyosarcoma (article in Japanese); *Nippon Ronen Igakkai Zasshi*. May ; 41(3): 339-43, 2004.
4. Gosset P, Lecomte-Houcke M, Duhamel A, Labat-Moleur F, Patey M, Floquet J, Vinnet G, Berger-

- dutrieux N, Cailou B and Franc B: 112 cases of sporadic and genetically determined pheochromocytoma : A comparative pathologic study. (article in French); *Ann Pathol*. Dec; 19 (6): 480-486, 1999.
5. Gutmann DH, Cole JL, Ponder BJ and Collins FS: Loss of neurofibromin in adrenal gland tumors from patients with neurofibromatosis type 1. *Genes chromosome cancer* ; 10: 55-58, 1994.
 - 6- Noriko Kimura, Toshiya Watanabe, Masayuki Fukase, Atsushi Wakita, Takao Noshiro and Itaru Kimura: Neurofibromin and NF1 Gene analysis in composite pheochromocytoma and tumors associated with von Recklinghausen's disease. *Mod. Pathol*; 15: 183-188, 2002.
 7. Hirsch NP, Murphy A and Radcliffe J: Neurofibromatosis: clinical presentations and anaesthetic implications; in *Br. J. anaesth*. Apr; 86(4): 555-64, 2001.
 - 8- Sano F, Fuji Kara N, Hirai K, Veki T and Kitamk. Pheochromocytoma associated with NF1: a report of 2 cases (article in Japanese). *Hinyokika Kyo*, Dec; 51 (12) 793-5, 2005.
 9. Kamiya J, Yasui T, Suzuki O, Nakamoto H, Maruyama T, Kawamura Y, Ookawa H, Kiryu Y and Shimizu K.: Von Recklinghausen's disease associated with pheochromocytoma : An autopsy case report and review of 24 cases in the Japanese literature, *gan No Rinsh* (Japanese journal of cancer clinics), Nov; 32(14): 1872-8, 1986.
 10. Rabii R, Fekak H, Moufid K, Joual A, Bennani S, el Mrini M and benjelloun S. Pheochromocytoma and von Recklinghausen's disease . *Ann Urol (Paris)*. Jul; 36(4): 254-7, 2002.
 11. Ventura A, Riberio J, Murinello A, Amado L, Morgado A, Guerra C, Murinello F, Silva J and Mota JA.: Von Recklinghausen neurofibromatosis and malignant pheochromocytoma: presentation of 3 cases (article in Portuguese). *Acta Med Port* . Mar-Apr; 2(2): 83-8, 1989.
 12. Walther MM, Herring J, Enquist E, Keiser HR and Linehan WM. Von Recklinghausen disease and pheochromocytoma. *J Urol*. Nov; 162(5): 1582-6, 1999.
 13. Zoller ME, Rembeck B, Oden A, Samuelsson M and Angervall L.: Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. *Cancer*. Jun 1; 79(11): 2125-31, 1997.