ORIGINAL ARTICLE

Secondary Amyloidosis of the Conjunctiva and Mucosa of Upper Respiratory Tract Associated with Renal Cell Carcinoma: Case Report and Review of Literature

Ibrahim T M** *MBBS, FWACP, EDIM, MACP* * Iheonunekwu N** *MBBS, DM. MACP*

**Consultant Physician, Department of Medicine, Peebles Hospital, Roadtown,Tortola, British Virgin Islands*
***Consultant Physician and Nephrologist, Department of Medicine, Peebles Hospital, Road Town, Tortola, BVI*

Abstract

***Background**: Secondary amyloidosis of the conjunctiva and respiratory mucosal antedating cancer is very rare. We present a case illustrating this rare association in order to draw the attention of clinician to the association between secondary amyloidosis and cancers.*

***Method:** We present a 72 yrs old woman with secondary amyloidosis of conjunctiva and the mucosa of the nasal and para- nasal sinuses secondary to renal cell carcinoma a common medical masquerader. She presented with bleeding fleshy growth on the conjunctivae and in the nostrils and the para nasal Sinuses. She also had a left renal mass. The histology of the conjunctivae and mucosa lesions revealed secondary amyloid deposit in the tissues. While the renal biopsy tissue showed papillary renal cell carcinoma.*

***Conclusion**: We suggest therefore, that secondary Amyloidosis including those of rare sites should be suspected in patients with chronic inflammations and malignancies. And it is also pertinent to look for malignancy in cases of unexplained reactive amyloid.*

Date Accepted for publication: 11th March 2009
Nig J Med 2009; 172 - 174

Introduction

Amyloidosis occurs as a result of the deposit of abnormal proteinaceous insoluble fibrils in various tissues and organs. And in most cases adversely affect the functions of the organs involved [1-3].The aetiopathogenesis of amyloidosis varies with the type of amyloid that is deposited. Secondary amyloidosis is well studied and various causes as been identified. This includes chronic inflammations and some malignancies such as renal cell carcinoma (RCC). Secondary amyloidosis is a recognized paraneoplastic presentation of RCC and in some cases may antedate the cancer [1-6]. We hereby present a case of RCC with secondary amyloid deposit in unusual sites.

Case Report

GR was a 72 yr old woman with the history of hypertension on amlodipine. She was referred to us at the Peebles hospital, Tortola in British Virgin Islands from the primary healthcare clinic with a year history of recurrent epistaxis from the left nostril, easy bruising, and swelling of the left leg and a fleshy growth in her eyes, the left more involved than the right. She had had surgery to the right eye some months before presentation with no significant improvement. She also has progressive hearing loss, which was worse in the right ear. No other significant symptoms except for one episode of frank total haematuria, which she had while on admission. She never smoked cigarettes or drank alcohol. Her sister has dermatitis herpetiformis, diabetes mellitus and hypertension. On examination her vital signs where as follows: HR=89/min, BP=130/79 mmHg, $\%SPO_2$= 92 %(RA) and BT=99.0 ^{O}F.She had periorbital bruises and ecchymotic patches on the arms and thighs. There was an extensive fleshy growth in the conjunctiva more florid on the left (figure1). The left nostril was blocked with a fleshy growth that bled intermittently on minimal contact. She had coarse crackles posterobasally. The other systems were essentially normal except for bilateral conduction deafness and nasal speech. The CBC showed anaemia with mildly low platelet count. The E/U/Cr were normal but the Ca^{2+} and alkaline phosphates were elevated at 13.2 mg/l and 265 U/l respectively. She had coagulopathy as she was not on any anticoagulant. The chest x-ray showed reticulonodular shadows in the lungs while the CT scan of the chest showed bilateral pleural effusion. The CT scan of the abdomen showed an exophytic mass on the left kidney with hydronephrosis and calcification. The CT scan of the para-nasal sinuses showed prominence of the lymphoid tissue, opacification of the air cells and occlusion of the left nostril by a soft tissue. The histopathologic findings of the renal mass that was removed laparoscopically, and that of the conjunctiva

Correspondences to: ***Dr Tunde Maiyaki Ibrahim,*** *Email: imaiyaki@yahoo.com 61358322322(work) 61358315875(home)*

tissues taken at a referred hospital, was consistent with papillary renal cell carcinoma and secondary amyloidosis respectively. The lesions on the conjunctiva, left nostril and the para nasal sinuses regressed considerably after the RCC was removed.

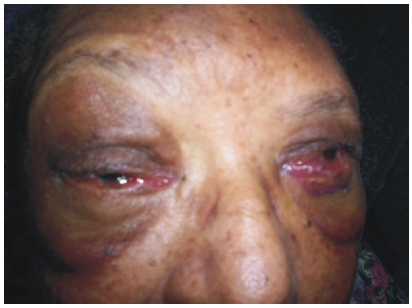

Figure 1: Secondary amyloid deposit on the conjunctiva.

Discussion

Amyloidosis is a disease in which abnormal proteinaceous insoluble fibrils are deposited in extracellular tissues of various organs. Amyloidosis is classified based on the type of protein fibril deposited in the tissues. The commonest type is the monoclonal immunoglobulin light chain (AL) amyloidosis associated with multiple myeloma and other gammopathies. The other important forms of amyloidosis are hereditary and secondary amyloidosis due to the deposition of transthyretin and serum amyloid A protein (SAAP) respectively both of which are acute phase reactant proteins [1-4]. This paper will concentrate on secondary amyloidosis, which is illustrated by the case being presented.

Secondary amyloidosis is due to the deposition of SAAP, which is produced as a result the action of inflammation responsive transcription factor called serum amyloid A activating factor 1 (SAF-1) [7] . The chronic inflammatory conditions and probably malignancies which lead to secondary amyloidosis stimulate the production of SAF-1 by releasing cytokines such as TNF alpha and interleukin 6.The fibrillated SAAP fibrils are subsequently coupled with the non fibrilar protein called pentraxin to form the secondary amyloid protein, which is then deposited in various tissues and organs [2-4,7].

Secondary amyloidosis is commonly associated with chronic inflammatory conditions and malignancies. Examples of these conditions are rheumatoid arthritis, ankylosis spondylitis, juvenile idiopathic arthritis, ulcerative colitis, familial Mediterranean fever, bronchiectasis, RCC, Lymphomas, breast cancer and leiomyosarcoma [1-6, 8-10]. RCC is one of the most common cancers that are associated with secondary amyloidosis. This is not surprising as RCC produces many biologically active substances. Some of these substances, such as the TNF alpha, interleukin 6 and other cytokines lead to the production of SAAP via the activation of the SAF-1. [5, 11-13] These are also involved in the other paraneoplastic syndromes associated with RCC.

Paraneoplastic syndromes are present in up to 20% of RCC. These include endocrine and metabolic disorders such as hypercalcemia, amyloidosis, cachexia, pyrexia and non metastatic hepatic dysfunction.

Secondary amyloidosis is deposited in many tissues and organs except the heart and this leads to organ enlargement and dysfunction [2, 3, 14-15]. The organs most commonly involved by secondary amyloidosis are the kidneys, skin, mucosa of the respiratory and gastrointestinal tracts, and the blood vessels. Secondary amyloid deposits in various ocular tissues have also been reported with the involvement of the cornea, conjunctiva, sclera, retinal and extraocular muscles reported in literature. The ocular involvement usually present as ocular masses, extraocular muscles infiltration and bleeding [16-19].

The diagnosis of amyloidosis generally involves having a high index of suspicion but the confirmation requires various laboratory techniques. The simplest and easiest is to stain the biopsy tissue with Congo red, or hematoxylin and eosin stains.

More complex and sophisticated methods include the use of radioactive123 iodine and other nuclear tracers bound SAP. These tests are said to be extremely useful and safe. They provide very specific non-invasive quantitative scintigraphic imaging of systemic amyloid deposits. Auto-antibodies to seek SAAP in tissues, various forms of fluorescences spectroscopes, electrophoreses and amino acid sequence analysis have also been used to diagnosed amyloidosis [2, 20-26].

There is no satisfactory definitive treatment for amyloidosis yet and it is usually a slowly progressive disease. But some cases of secondary amyloidosis regress or even disappear with successful treatment of the underlying condition. Many treatment trials with various forms of anti-inflammatory agents have been reported. Metyas et al [27] reported the first successful treatment of secondary amyloidosis associated with familial Mediterranean fever with infliximab an anti TNF antibody. Similarly Okuda and Takasigi [28] reported the successful treatment of secondary amyloidosis

complicating juvenile idiopathic arthritis with interleukin 6 receptor antibody tocilizumab. There is also a promising prospect of successful treatment of secondary amyloidosis with anti inflammatory agent dimethyl sulfoxide. Amemori et al [29], observed that oral dimethyl sulfoxide is an effective treatment of SAAP associated amyloidosis, especially in those with gastrointestinal mucosa and early renal involvement.

Other anti inflammatory agents such as, chlorambucil, colchine, nicotine and non steroidal anti-inflammatory analgesics, that have been tried in the treatment of beta-amyloid associated with Alzheimer's disease, and AL amyloidosis associated with multiple myeloma may also be useful in the treatment of secondary amyloidosis [2, 3, 30-32].

References

1. Comenzol RL. Amyloidosis. Curr Treat Options Oncol 2006, 7; 225-36
2. Sipe JD, Cohen AS . Amyloidosis. Harrison's Principle of Internal Medicine 15th ed ;2482- 1979
3. Cohen AS, Sipe JD. Amyloidosis. Clinical Immunology RR Rich et al ed .St Louis, Mosby Year Book 1995;1264-1272
4. Benucci M, Maniscalchi F, Manfredi M. Secondary amyloidosis complicating rheumatoid arthritis, prevalence study in Italian population. Recenti Prog Med 2007; 98 : 16-29
5. Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. Semin Urol Oncol 1996;14:216-222
6. Zhul LC, Sidhu GS, Yee HT, Cassai ND, Goldfarb DS, Wieczorek RL. AA- type amyloidosis associated with non-Hodgkin's lymphoma: a case report. Hum Pathol 2004; 35: 1041-1044
7. Ray A, Shakya A, Kumar D, Benson MD, Ray BK. Inflammation-responsive transcription factor SAF-1 activity is linked to the development of amyloid A amyloidosis. J Immuno 2006; 177:2601-2609
8. SomerTP, Tornroth TS. Renal adenocarconima and systemic Amyloidosis.Immunohistochemical and histochemical studies.Arch Path Lab Med1995; 109:571-574
9. Onishi S, Hojo N, Sakai L, Matsumato T, Watanabe A, Miyazaki T, Ito MR, Nose M, Fujita S. Secondary amyloidosis and eosinophilia in a patient with uterine leiomyosarcoma. Jpn J Clin Oncol 2005; 35:617-621
10. Atanasova P, Milkov V. Para-amyloidosis in 2 patients with malignant diseases. Vutr Boles 1985; 24: 97-99
11. Marshall FF, Walsh PC, Extra renal manifestations of renal cell carcinoma.J Urol 1977; 117: 439-440.
12. Sufrin G, Ghasan S, Golio A, Murhhy G. Paraneoplastic and serologic syndromes of renal cell carcinoma. Semin Urol 1989;7:158-71
13. Palapattu GS, Kristo B, Rajfer J. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. Rev Urol 2002; 4:163-170
14. Sufrin G, Murphy GP. Humoral syndromes of renal adenocarcinoma in man. Rev Surg1997; 34:149-166.
15. Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspect of systemic amyloid disease. Biochem Biophys Acta 2005;1753:11-22
16. Landa G, Aloni E, Milshten A, Marcovich A, Mozes M, Polleck A. Eyelid bleeding and atypical amyloidosis. Am J O thalmol 2004;138:495-496
17. Okamoto K, Ito J, Emura J, Kawasaki T, Furusawa T, Sakai K, Tokiguchi S. Focal orbital amyloidosis presenting as rectus muscle enlargement: CT and MRI findings. Am J Neuroradiol 1998;19:1799-1801
18. Samz-Estebam A, Saornil Alvarez MA, Mendez-Diaz MC, Blanco- Mateos G. Primary localized conjunctiva amyloidosis: two case reports.Arch Soc Esp Oftalmol 2005;80:49-52
19. Lee HM, Naor J, DeAngelis D, Rootman DS.Primary localized conjunctiva Amyloidosis presenting with recurrence of sub conjunctiva hemorrhage. Am J Ophthalmol 2000; 120: 245-247
20. Strege RJ, Seager W, Linke RP. Diagnosis and immunohistological classification of Systemic amyloidosis: Report of 43 cases in an unselected autopsy series. Virchows Arch 1998;433:19-27
21. Pepys MB. Pathogenesis, diagnosis and treatment of systemic amyloidosis. Philos Trans R Sco Lond Bb Biol Sci 2001; 356:203-210
22. Fujihara S. Differentiation of amyloid fibril proteins in tissue sections. Two simple and reliable histological method applied to fifty-one cases of systemic myloidosis. Acta Pathol Jpn 1982; 32:771-782
23. Hoshii Y. Histopathological diagnosis of amyloidosis. Rinsho Byori 2006; 54: 513-518
24. Hazenberg BP, VanRijswijk MH, Piers DA, Lub-DE hooge MN, Velleng E, Haagsma FB, Hawkins PN, Jager PL. Diagnostic performance of 123I labeled serum amyloid P Component scintigraphy in-patient in patients with amyloidosis. Am J Med 2006; 119: 15-24
25. Gillmore JD, Hawkins PN, Pepys MB. Amyloidosis: a review of recent diagnostic and Therapeutic development. Br J Heamatol 1997; 99: 245-56
26. Munishkina LA, Fink AL. Fluorescence as a methods to revealed structures and membrane- interactions of amyloidogenic proteins.Biochim Biophys Acta 2007;12-14
27. Metyas S, Arkfeld DG, Forrester DM, Ehresmann GR.Infliximab Treatment of Familial Mediterranean Fever and Its Effect on Secondary AA Amyloidosis. J Clin Rheumatol 2004 ;10: 134-137
28. Okuda Y, Takasugi K. Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. Arthritis Rheum 2006 ; 54: 2997-3000
29. Amemori S, Iwakiri R, Endo H, Ootani A, Ogata S, Noda T, Tsunada S, Sakata H, Matsunnaga H , Mizuguchi M, Ikeda Y, Fujimoto K . Oral dimethyl sulfoxide for systemic amyloid A amyloidosis complication in chronic inflammatory disease: a retrospective patient chart review. J Gastroenterol 2006 ;41: 444-9
30. Tan SY, Pepys MB, Hawkins PN. Treatment of amyloidosis .Am J Kidney Dis 1995; 26: 267-285
31. Zeng H, Zhang Y, Peng L, Shao H, Menon NK, Yang J, Salomon AR, Friedland RP, Zagorski MG. Nicotine and amyloid formation. Biol P sychiatry 2001; 49: 248-257
32. Yan Q, Zhang J, Liu H, Babu-Khan S, Vassar R, Biere AL, Citron M, Landreth G. Anti-inflammatory drug therapy alters beta- amyloid processing and deposition in animal model of Alzheimer's disease. J Neurosci 2003;23:7504-7509