CLINICOPATHOLOGICAL CONFERENCE: AMYLOIDOSIS AND LIGHT CHAIN MYELOMA IN A 68-YEAR-OLD MAN

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Summary

A 68-year-old man presented with chest pain, weight loss, sore tongue, thigh claudication and bilateral carpal tunnel syndrome. Systemic amyloidosis and lambda light chain myeloma were diagnosed. Amyloid deposition was found in tongue, synovium of carpal tunnel, kidneys, lungs and subcutaneous fat. Non-amyloid needle-shaped crystals with periodic structure were found in renal tubules. While it was evident that our patient had myeloma-associated amyloidosis, the aetiological significance of silicosis, tuberculosis and hepatitis B in this patient were discussed. A total of five patients with amyloidosis has been diagnosed in this hospital in the past two years, suggesting that the condition may not be rare among Chinese. Literature on the epidemiology of amyloidosis among Chinese, as well as the diverse manifestations of amyloidosis were reviewed. A heightened awareness among doctors is required to diagnose this multi-system disorder early.

Case Report

A 68-year-old man presented to our hospital on 20.5.1994 with a 2-month history of intermittent constricting chest pain, which radiated to his back, was posture-related, but unrelated to exertion or meals. It started off in mid-March 1994 with a sudden acute upper back pain while he attempted to get out of bed to toilet. He also complained of tightness over buttocks with prolonged walking. While walking uphill to visit the tomb of his recently deceased mother during the Ching Ming Festival, he was interrupted by severe right hip pain. He had sought medical advice for painful and swollen tongue, but was reassured that he had aphthous ulcer. However, the pain and swelling persisted; he could not speak clearly and he could tolerate fluid diet only. His appetite was reduced and he had a 10-kg weight loss in two months. He also complained of epigastric discomfort with tarry stool for one month.

Since August 1993 he noticed numbness of both hands with his little fingers spared, worst with the middle fingers, more severe on the right side, wakening him up in the middle of night, and relieved by hanging his arms by the bed side and shaking his hands. His workmates remarked that his hands were cold to touch. He had been working as a stone-cutter for thirty years, but he had to quit his job in October 1993 because of distressing numbness of his hands on lifting up heavy concrete. He had consulted doctors for the hand numbness, for which he had been given injections into both wrists, but without much relief.

He had a chest radiograph taken in a chest clinic in January 1994 for 1-month history of severe cough, and he was reassured that he had nothing serious. The cough subsequently subsided after self-treatment with herbs. His past health was good otherwise and he had no known history of tuberculosis or syphilis. He had been a chronic smoker till March 1994.

Examination revealed that he had pallor. The blood pressure was 110/70mmHg, pulse 72/minute, and respiratory rate 20/minute. His mental status was normal. His speech was slurred and slow but was readily comprehensible if listened carefully. His tongue was enlarged with nodular growths over both sides (Figure 1). Swallowing was difficult. His cranial nerve examination was otherwise normal. His history suggested bilateral carpal tunnel syndrome, and was supported by the findings of reduced pin-prick sensation over the radial three-and-a-half fingers of both hands, and a positive Tinel's sign. Depigmented scars were noted over both wrists, probably resulting from previous steroid injections.

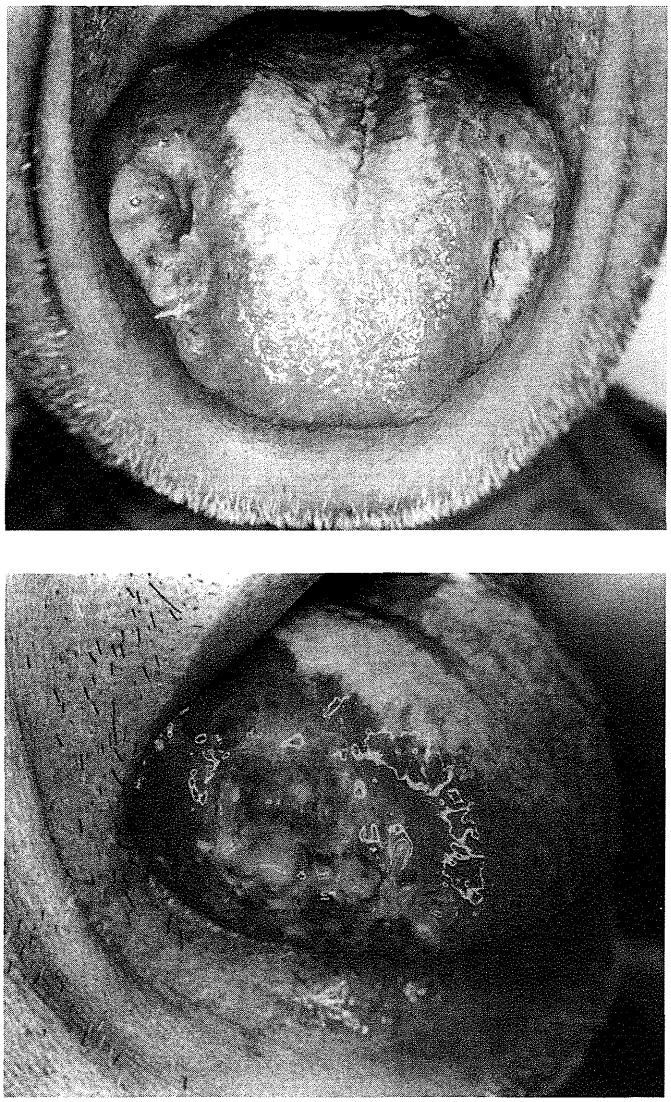

Figure 1. Anterior and lateral views of the enlarged tongue with bilateral nodular growths; biopsies have been done on both sides.

Reduced pin-prick sensation in a stocking distribution over both feet was detected, suggesting peripheral neuropathy of lower limbs. Localized tenderness was elicited over his dorsal spine. There was no hepatosplenomegaly nor lymphadenopathy, and per-rectal examination revealed no melena.

Investigations on admission revealed hypercalcaemia (Ca 3.0 mmol/l, PO4 1.32mmol/l) and hyperuricaemia (0.65mmol/l). Renal function test result was Na 139mmol/l, K 4.5 mmol/l, urea 8.9 mmol/l, creatinine 221μmol/l. Erythrocyte sedimentation rate (ESR) was raised at 70 mm/h. He had macrocytic anaemia (Hb 9.7g/dl, MCV 99fl) with normal white cell and platelet counts. Stool for occult blood was positive. The liver function test revealed mild hypoalbuminaemia (33g/l), raised alkaline phosphatase (203iu/l) and alanine aminotransferase (54iu/l); the serum globulin was 27g/l and bilirubin 9μmol/l. The HBsAg was negative while anti-HBc was positive. Fasting blood glucose was 3.9mmol/l and the arterial blood gases were normal. Electrocardiogram revealed normal sinus rhythm and normal voltage. The tuberculin test was negative. Sputum and urine specimens revealed no acid-fast bacilli on smear or culture. Ultrasonogram of the kidneys and liver were normal.

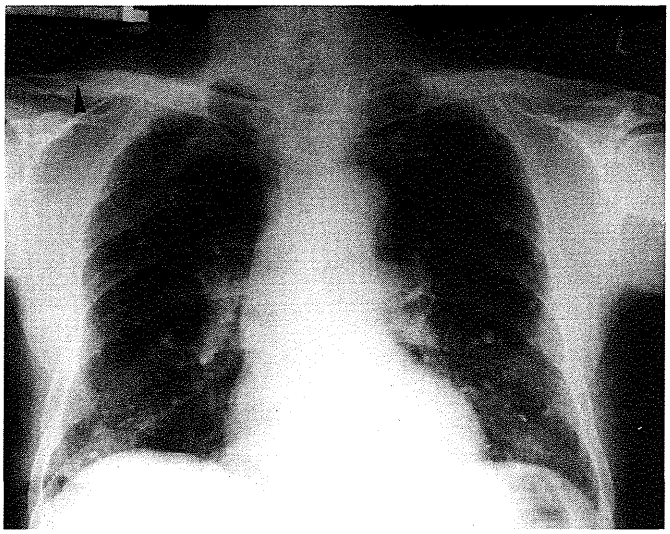

Figure 2. Chest X-ray showing bilateral multiple fibrocalcified foci, background nodularities and fibrotic change over right apex. Note lytic lesion (arrowhead) with well-defined border over right clavicle.

Chest X-ray(Figure 2) was reported as "bilateral multiple fibrocalcified foci and background nodularities with fibrotic opacity in right upper zone suggestive of pneumoconiosis with progressive massive fibrosis". X-ray of his thoracic spine revealed collapse of T5 vertebra with intact endplate, which would account for his chest pain. Skeletal survey(Figure 3) demonstrated generalized osteopenia, as well as focal areas of osteolytic lesions at both humerus and femora. The skull X-ray showed no bony lesion.

Tongue biopsy(Figure 4) revealed amyloidosis. Nerve conduction study confirmed bilateral carpal tunnel syndrome and peripheral neuropathy of both lower limbs. His hand numbness was relieved by carpal tunnel release, which revealed amyloid in the resected synovial tissue. The echocardiogram showed an ejection fraction of 60% and no evidence of restrictive cardiomyopathy.

Further work-up showed a 24-hour protein excretion of 2.79g and the urine contained Bence Jones protein. Serum immunoglobulin pattern revealed reduction of immunoglobulins A(0.35g/l), G(5.71g/l) and M(0.19g/l) respectively. Serum protein electrophoresis (Figure 5a) showed a sharp abnormal paraprotein band of 6g/l in the

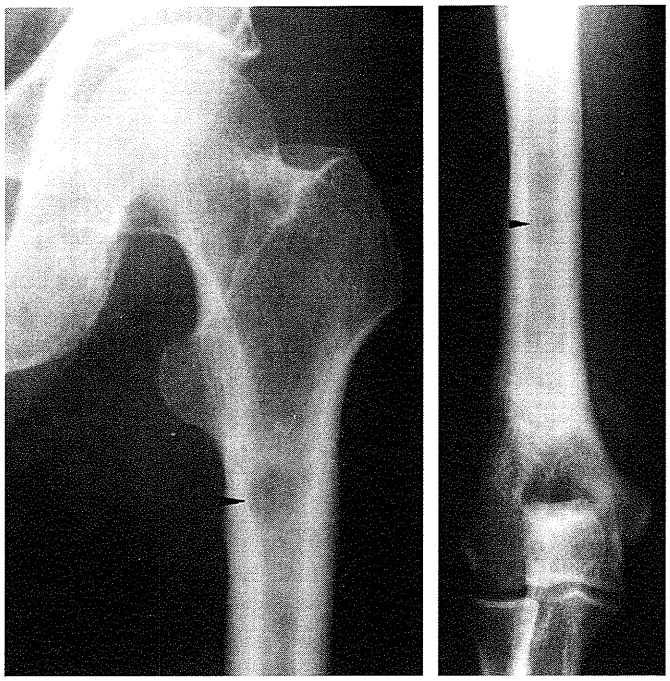

Figure 3. Skeletal survey showing osteopenia and osteolytic lesions (arrowheads) at humerus and femur.

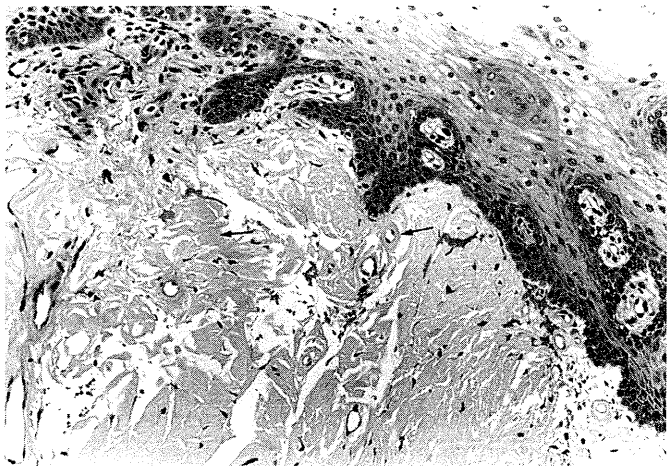

Figure 4. Section of tongue biopsy stained with Congo red showing heavy deposition of congophilic material(arrows) in subepithelial stroma, both perivascular and interstitial. The congophilic material showed apple-green birefringence when viewed under polarized light, consistent with amyloid.

beta/gamma region with immune paresis. Urine protein electrophoresis (Figures 5b, 5c) also showed a sharp abnormal paraprotein band which migrated to the same position in the gel as that of serum. Immunofixation electrophoresis revealed the presence of lambda free light chains in both urine and serum.ß$_2$-microglobulin was raised at 12.4µg/ml(normal < 2µg/ml). Bone marrow

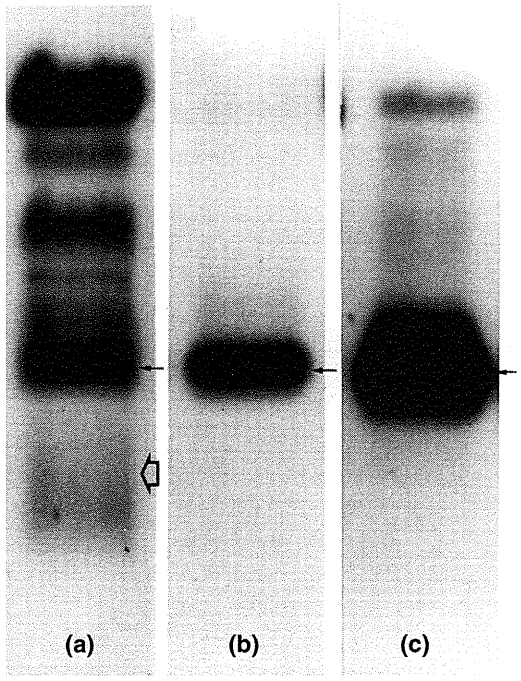

Figure 5. Protein electrophoresis of the serum (a), urine concentrated 20x (b), and urine concentrated 100x (c) showing a monoclonal paraprotein band (black arrows) in the beta/gamma region that has the same electrophoretic mobility in each sample. By immunofixation, these bands were identified as free lambda light chains. Note immunoparesis (white arrow) in the serum sample. The pattern in sample (c) shows anodal slurring of the paraprotein band which is due to overloading effect by the large amount of paraproteins.

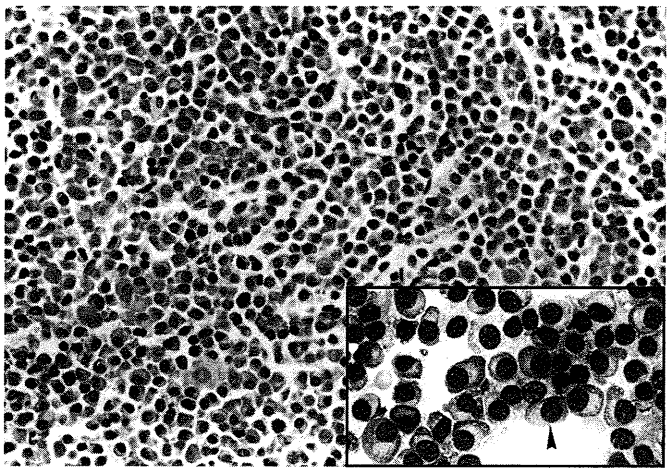

Figure 6. Bone marrow aspirate biopsy showing large sheet of atypical plasma cells. Inset: plasma cells, some with prominent nucleoli(arrowhead)

aspiration(Figure 6) and biopsy showed more than 80% replacement with abnormal plasma cells.

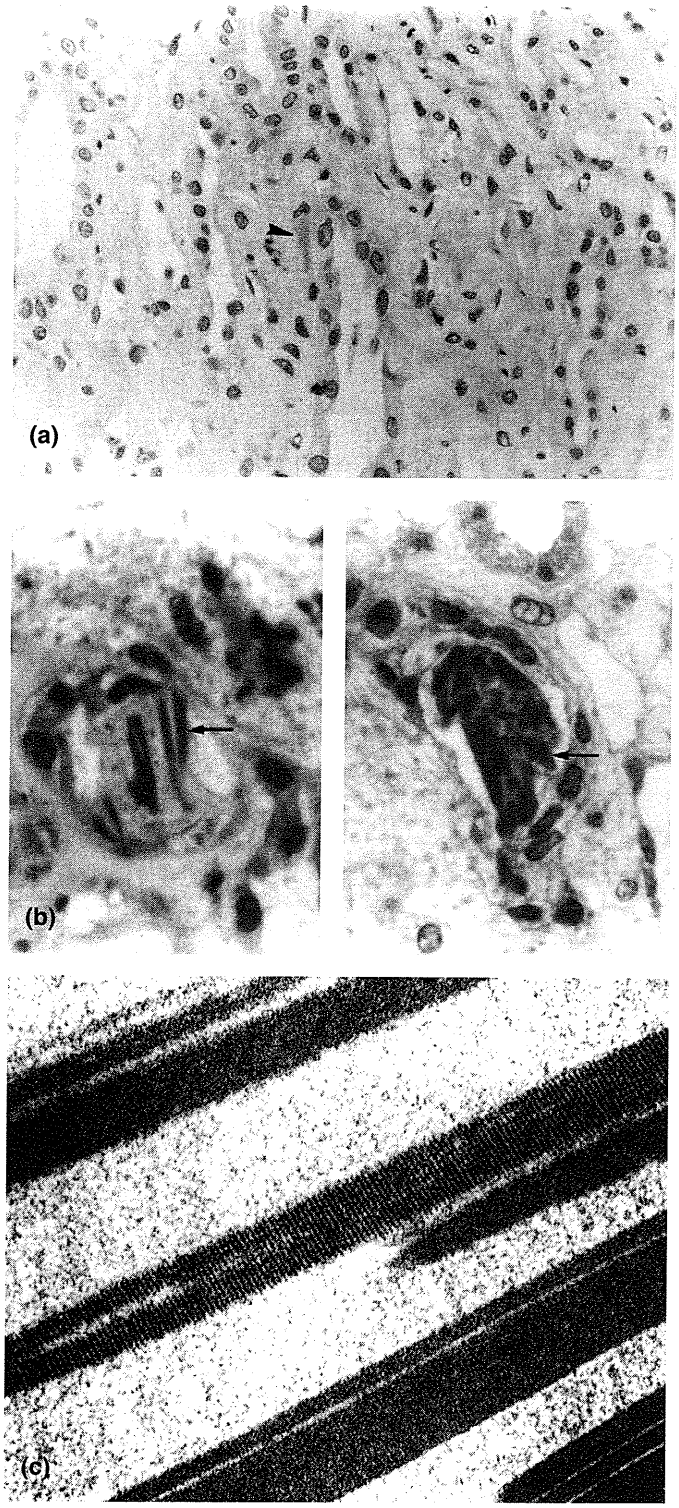

Figure 7. Renal biopsy showing (a) amyloid (arrowhead) deposition in interstitium and (b) hyaline cast with needle-shaped and rhomboid-shaped crystals (arrows) within tubules. (c) Electron microscopy showing needle-shaped crystalloid material with periodicity

Immunohistochemical stains performed on paraffin sections showed negative reactivity for immunoglobulin heavy chains IgG, IgA and IgM, while definite λ light chain restriction can be demonstrated. Thus, the patient was thought to have λ light chain multiple myeloma.

He was rehydrated with normal saline, with improvement of renal function after 5 days (urea and creatinine fell to 5.4mmol/l and 126μmol/l respectively) and reduction in hypercalcaemia (Ca fell to 2.64mmol/l on 25.5.1994). However serum calcium climbed up to 2.94mmol/l on 3.6.1994. Chemotherapy was started on 4.6.1994 with melphalan 8mg and prednisolone 15mg qid for 7 days. The serum calcium returned to normal (2.56mmol/l) on 11.6.1994. Subsequent course was however complicated by gram negative septicaemia *(Klebsiella species)*. His renal function deteriorated (urea 21.6mmol/l, creatinine 425μmol/l). Ultrasound-guided renal biopsy(Figure 7) showed amyloidosis and cast nephropathy consistent with multiple myeloma; needle-shaped and rhomboid crystals were noted in the tubular lumen. He developed haemorrhagic zoster over the left L1 and L2 dermatomes. He finally succumbed on 28.6.1994.

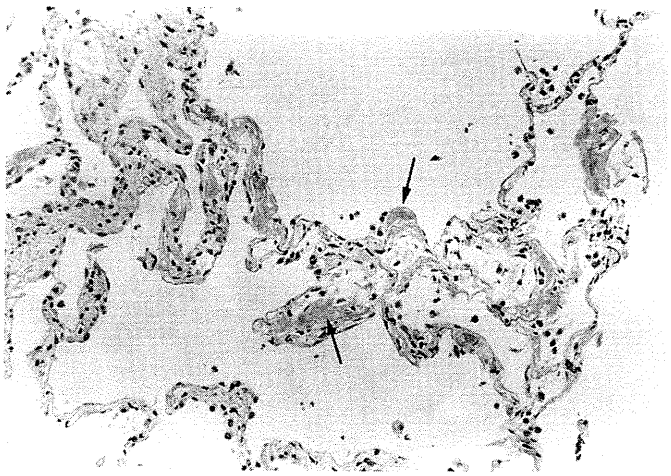

Figure 8. Lung biopsy showing amyloid in interstitial tissue within the interalveolar septa(arrows).

Consent for autopsy was not obtained. Paramortem liver and lung biopsies were done. The lung biopsy(Figure 8) showed depositions of amyloid in the peribroncheal interstitial tissue as well as the interalveolar septa. No myeloma cell infiltration was seen in the lung. There was no amyloid nor any other significant pathology within the liver parenchyma, though amyloid was present in a detached piece of subcutaneous fibro-fatty tissue.

Discussion

The word "amyloid" was first coined to describe "waxy, eosinophilic" tissue deposits, which when stained with Congo red, gave an apple-green birefringence under

polarized light. It is now known that amyloid accumulation is a syndrome rather than a single disease, resulting in the deposition of twisted ß-pleated sheet fibrils formed from proteins of great chemical diversity[1]. It has been shown that the staining and optical properties previously used to define amyloid fibrils are due to their ß-pleated sheet conformation, which led to the insolubility of the fibrils, and thus to their potentially lethal nature when deposited in tissues.

The incidence of systemic amyloidosis was reported to be 0.6 to 0.7% in one hospital population[2] and the incidence of primary systemic amyloidosis is 8.9 per million per year in Minesota in the United States.[3]. Though amyloidosis is a common disease in the West, few cases have been reported in Chinese. Unfamiliarity with this condition can pose a diagnostic problem to various specialists. Tay[4] reported a 74-year-old Singaporian Chinese who had been investigated for over three years by general practitioners, ophthalmologists, ear-nose-throat surgeons, dermatologists, haematologists and physicians for purpura and skin nodules over the face before the diagnosis of primary systemic amyloidosis was finally established. A 10-year retrospective review[5] in a Taiwan general hospital identified 12 Chinese with primary amyloidosis including one case of λ light chain myeloma, the mean age of onset being 53.3 years(range: 32 to 65 years) . Liu et al.[6] retrospectively reviewed 14 Chinese with renal amyloidosis(11 primary, 3 secondary) over a 25-year period in a Beijing university hospital, and the mean age was 48.2 years(range: 25 to 66 years). 7 of the 14 cases were diagnosed within the last two years of their study and Liu thought that the disorder was not rare in China. In 1979, Ho et al.[7] reported two elderly Chinese(one aged 74 years) with amyloidosis diagnosed in our hospital though no firm conclusion can be made on whether they were primary or secondary. A computer search of our hospital record from January 1993 to December 1994 identified 5 Chinese, including the present one, with amyloidosis diagnosed, four of whom had associated monoclonal paraproteins in serum or urine while the other one had raised immunoglobulin M and reduced immunoglobulin G in serum. Their age ranged from 58 to 74 years(mean 66 years). The catchment population of our hospital for 1993-1994 was around 0.8 million so that the incidence of amyloidosis in our locality was 3.1 per million per year. We think therefore amyloidosis may not be that rare among Chinese. These five patients have presented to various specialists at different times: emergency physicians(for acute back pain), chest physicians(for chronic cough), orthopaedic surgeons(for hand numbness, gouty arthritis), surgeons(for gastro-intestinal bleeding, tongue nodule, head injury after fall) and physicians(for proteinuria, nephrotic syndrome, renal impairment, chest pain, heart failure, purpura, anaemia, dysphagia). As amyloidosis is a multi-system disorder, all doctors of various specialties or sub-specialties will be seeing patients with amyloidosis and, therefore, should recognize it.

Though our patient presented with the classic features of systemic amyloidosis: bilateral carpal tunnel syndrome and macroglossia, the correct diagnosis had been delayed by the fact that his hand and tongue problems had been dealt with separately by different doctors at different times and a synthetic whole-person approach had not been adopted. The diagnosis of amyloidosis was established by the presence of amyloid in tongue, carpal ligaments and kidneys. There were also features suggestive of myeloma: bone pain associated with osteopenia, multiple osteolytic lesions, hypercalcaemia and high ESR. The diagnosis of light chain myeloma was made from: monoclonal λ light chain paraprotein in serum and urine, suppressed serum immunoglobulins, increased numbers of immature plasma cells in the bone marrow, and lytic bone lesions. Light chain immunoglobulins, being of low molecular weight, are filtered into the urine, and thus usually do not accumulate in the serum unless severe renal failure is present[8,9]. The presence in the serum of significant light chain immunoglobulin in the absence of severe renal failure at the initial presentation of our patient is indicative of a high tumour cell burden, which is also evidenced by the presence of osteolytic lesions[10], the high percentage of plasma cells in the bone marrow, the grossly elevated urine protein excretion and the highly elevated serum $ß_2$-microglobulin in our patient[11].

The present case is an example of myeloma-associated amyloidosis. Amyloidosis develops in 6-15% of myeloma patients[12], and is more prevalent in light chain myeloma (20-24%)[13,14]. Studies[15] have demonstrated that light chains of immunoglobulins could be converted into ß-pleated sheet fibrils, supporting the pathogenetic role of light chains in systemic amyloidosis. The observation that only 20-24% of light chain myeloma patients develop amyloidosis suggests that not all light chains are "amyloidogenic". There is also a predominance of λ type light chain immunoglobulin in patients with myeloma-related amyloidosis[3,16,17]: two-thirds of myeloma patients complicated by amyloidosis have λ light chains (characteristically $λ_{VI}$ subclass), whereas two-thirds of myeloma patients uncomplicated by amyloidosis have κ light chains. The finding of λ chains, as in our patient, should therefore raise the suspicion of amyloidosis.

Carpal tunnel syndrome was the earliest presenting symptom in our patient, but amyloidosis as the underlying cause was made only 10 months later. In Kyle's series[18], carpal tunnel syndrome was present in 24% of primary amyloidosis patients (38% for those associated with myeloma) and the median duration of carpal tunnel syndrome before diagnosis of amyloidosis was 12.5 months. While peripheral neuropathy is common in primary and familial amyloidosis syndromes, there have been only two previous reports of peripheral neuropathy

complicating light chain myeloma[19,20], one with and one without amyloidosis. His hip pain on exertion was likely due to claudication of thigh muscles. Claudication in amyloidosis was thought to be due to the deposition of amyloid in skeletal muscle vasculature leading to a diminished arteriolar dilator capacity and compromised blood supply during exertion[21,22].

Macroglossia was observed in 22% of primary amyloidosis patients, and is more common in those with myeloma(32%) as compared to those without myeloma(19%)[18]. Amyloid involvement of the tongue in our patient has caused much distress and dysfunction, interfering with normal speech and swallowing. The slurred and slow speech might result in incomplete history recording and the consequent delay in diagnosis. Despite his slurred speech, this patient could nevertheless give a very accurate account of his symptomatology, including the detailed symptoms of carpal tunnel syndrome. He also has oro-pharyngeal dysphagia secondary to macroglossia. Macroglossia can sometimes be so severe as to cause airway obstruction, necessitating tracheostomy[23]. Gastrointestinal bleeding, an initial finding in our patient, is caused by amyloid deposition in the gastrointestinal tract[24].

Cough has been a prominent symptom in our patient. Amyloidosis of the lower respiratory tract can mimic carcinoma, pulmonary oedema, diffuse lung fibrosis, bronchiectasis, tuberculosis and other cardiothoracic diseases; so that a clinical diagnosis of pulmonary amyloidosis can be difficult[25,26]. Although two radiological patterns, interstitial or nodular, have been described[26], they were not diagnostic. The chest radiograph of our patient showed multiple nodular calcifications and has been reported as pneumoconiosis, which is compatible with his long history of exposure to silica. However, the characteristic egg-shell calcifications of silicosis were absent from his chest film. Furthermore, up to one-third of the nodules in amyloid lung can have calcifications[25]. The limited para-mortem lung biopsy revealed amyloidosis but no evidence of silica particles.

Various authors have emphasized that amyloidosis should be suspected in any patient aged over 50 years presenting with a new onset of proteinuria or nephrotic syndrome[27,28]. The prominence of renal functional impairment in light chain myeloma has also been emphasized[13] as a common presenting feature and an important cause of death. A number of factors have been incriminated in myeloma nephropathy: Bence Jones proteinuria, dehydration, hypercalciuria, hyperuricosuria, plasma cell infiltration, pyelonephritis and amyloidosis[13]. 10% of myeloma patients are reported to have "myeloma nephrosis"[29], a condition in which tubular lumens are occluded by dense eosinophilic crystalline casts surrounded by leucocytes and giant cells. In-vivo and in-vitro studies[30,31] have demonstrated the presence of amyloid fibrils in myeloma casts, and their production by selective proteolysis of specific Bence Jones proteins by renal-tubular epithelial cells. Hirota[32] first reported two different types of deposition in the kidneys of a Japanese woman with lambda light-chain myeloma: (1) AL-type amyloid, (2) non-amyloid light-chain crystals, which were needle-like or rhomboid in shape. It is of interest to note that our patient also showed two types of deposition(Figure 7).

Glenner[1] has discarded the terminology of "primary" and "secondary" in designating systemic amyloidosis. He reclassified systemic amyloidosis as (1) immunocyte-derived, which replaced the previous term "primary" to emphasize that this group is one of the monoclonal immunoglobulin deposition diseases, whether overt myeloma is present or not, (2) reactive, and (3) heredofamilial. It is clear that our patient belongs to the immunocyte-derived group. However, one might speculate whether his amyloidosis is reactive to silicosis or possibly tuberculosis, to which silicosis patients are prone. Though certain chronic inflammatory conditions such as rheumatoid arthritis have been documented to be associated with amyloidosis, the association of silicosis with amyloidosis has not been described to our knowledge. Tuberculosis is a well-known cause of reactive amyloidosis[33] as well as reactive plasmacytosis, and also has been shown to be associated with myeloma in epidemiology studies[34]. We have recently diagnosed multiple myeloma in a patient who developed pancytopenia during the course of anti-tuberculous treatment. Nevertheless we are unable to document any active tuberculosis nor such a history in our patient though his chest film can be compatible with old tuberculosis. Myelomatous bone involvement is usually associated with normal serum alkaline phosphatase. The raised serum alkaline phosphatase in our patient may be related to the compression fracture-collapse of T5 vertebra or to possible liver pathology. Though the restricted para-mortem liver biopsy was normal, the liver enzyme was mildly elevated. The anti-HBc was positive in our patient, indicating previous exposure to hepatitis B. The association of hepatitis B and amyloidosis in our patient can be coincidental since hepatitis B is common in Hong Kong; 76.8% of those over the age of 50 has some marker of previous hepatitis B infection and the carrier rate is 9.5%[35]. However, Ho et al.[7] reported two local Chinese with amyloidosis and positive HBsAg, and speculated on the aetiological significance of hepatitis B in amyloidosis. Interestingly, animal studies[32] revealed that amyloidosis of liver was more frequent in Chiba ducks infected with duck hepatitis B virus, though this did not reach statistical significance because of the small number studied and moreover genetic predisposition is also important in the pathogenesis[36,37].

Although there have been occasional reports of

myeloma-associated amyloidosis responding to melphalan-prednisolone treatment[38,39,40], the prognosis of such patients are poor in general. In one prospective randomised study on patients with primary systemic amyloidosis, the median duration of survival was 16 months in the group receiving melphalan and prednisolone[3]. Patients with myeloma-associated amyloidosis have shorter survival (4-7 months from diagnosis) when compared with either uncomplicated myeloma (20 months) or primary amyloidosis without myeloma (13 months)[13,18]. Patients with λ light chain paraprotein, as in our patient, have a shorter survival than those with κ light chain paraprotein[1]. Kyle concluded from a multivariate analysis[41] that the three unfavourable prognostic factors affecting 1-year survival in primary amyloidosis patients are congestive heart failure, presence of monoclonal light chains in the urine and marked weight loss. Our patient had two of the poor prognostic variables, i.e. monoclonal light chains in urine and significant weight loss. As mentioned previously, the tumour burden of our patient was high and this also accounted for his short survival.

It is our experience that myeloma patients usually present late to us, and consequently the prognosis is grave. Our patient may have developed idiopathic Bence Jones proteinuria or monoclonal gammopathies of uncertain significance(MGUS) long before evolving into amyloidosis with myeloma. The frequency of MGUS increases with age: 1 - 1.7% of those aged over 50 years and 3-5% of persons aged over 70 years have MGUS[42,43,44]. A recent community screening for MGUS in people aged 63-95 reported a prevalence of 10% and 2.7% in the United States and Japan respectively[45]. Studies have shown that up to one-quarter of cases of MGUS do progress to frank malignancy or systemic amyloidosis[46,47]; the previous term "benign monoclonal gammopathy" is thus misleading. Kyle[47] therefore suggested for those with MGUS, serial monitor of monoclonal paraprotein level and reevaluation are essential to detect malignant change or amyloidosis. However, 15% of patients with primary amyloidosis would have no detectable monoclonal paraproteins in both urine and serum; it has therefore been suggested that patients suspected of primary amyloidosis should have bone marrow taken for plasma cell and immunophenotyping to detect clonal excess[48]. With increasing awareness of this condition and improvement in test sensitivity in detecting paraproteins in urine, more cases of immunocyte-derived amyloidosis will be diagnosed earlier in future.

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