

# Human recombinant insulin and amyloidosis: an unexpected association

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## ABSTRACT

A 48-year-old patient with diabetes mellitus was treated with human (recombinant) insulin. He developed cutaneous amyloidosis twice at different locations where subcutaneous insulin had been injected. There were no signs of systemic amyloidosis. Additional pathological-anatomical investigations demonstrated insulin in one (the most recent) amyloid tumour. A limited number of similar cases have been reported in the literature, although mostly associated with porcine insulin. Cutaneous amyloidosis may be associated with local injections of human (recombinant) insulin. One should therefore also consider this diagnosis when finding tumours at sites where insulin has been injected.

## KEYWORDS

Diabetes mellitus, amyloidosis, insulin

## INTRODUCTION

Diabetes mellitus is a disease with a high incidence and prevalence. A large number of diabetes patients are being treated with subcutaneously injected insulin. Local complications include infections and the development of lipotrophic and lipohypertrophic areas. Cutaneous amyloidosis is not a frequent complication. In this manuscript we describe a patient who repeatedly developed amyloid tumours at insulin injection sites.

## CASE REPORT

A 48-year-old man had been visiting our outpatient clinic since 1995 for treatment of his type 2 diabetes mellitus.

His medical history included Horton's neuralgia (1982), an epileptic seizure during an episode of hypoglycaemia (1998) and essential hypertension (2003). The patient was initially treated with oral antidiabetic agents, but started insulin therapy in 1995 (Mixtard 30/70, twice a day). After 2000, the treatment was intensified to a regime of human recombinant insulin four times a day (Actrapid, Insulatard). His diabetes was generally well managed and no secondary complications had developed. In 2006, an abdominal tumour of 1 x 2 cm (left side, para-umbilical) was discovered. After excision, pathological-anatomical evaluation revealed an unexpected diagnosis: an amyloid tumour (although it was not clear whether it was an AA-amyloidosis or AL-amyloidosis). Extensive additional tests and examinations were performed, including computerised tomography (CT) scans of his thorax and abdomen, a PET scan, a bone marrow aspiration was obtained and a serum protein electrophoresis. No indications for a systemic amyloidosis were found and the final diagnosis was, therefore, a cutaneous amyloid tumour. The patient remained an outpatient and was checked

### What was known on this topic?

Insulin injections may be associated with (local) amyloidosis. Only few findings have been reported in the literature and these were generally associated with porcine insulin.

### What does this add?

This case report draws attention to amyloidosis as a rare side effect of – also human recombinant – insulin injections. This case report may also serve to remind physicians to consider this potentially serious side effect when finding a tumour at an insulin injection site.

frequently. In 2008 he complained of a tumour on his left arm. A core biopsy was taken. Again an amyloid tumour (nodular type) was diagnosed. The patient was treated surgically. The pathologist's conclusion (amyloid tumour, compatible with AL light chain) confirmed the diagnosis: microscopic evaluation showed local, poorly demarcated, areas consisting of dense collagenous tissue (*figure 1A*). After staining for amyloid (Congo red), these areas clearly showed apple-green bi-refringence using polarised light (*figure 1B*). This was confirmed in fluorescence after thioflavine staining. Immunohistochemical staining for insulin showed dark deposits in the same areas, which tested positive for the amyloid stains (*figure 1C*). The patient had developed a similar tumour twice in two years, which was remarkable in itself. Retrospectively, it was conspicuous that both amyloid tumours arose at insulin injection sites.

## DISCUSSION

### Amyloidosis in general

Amyloidosis is a disease characterised by extracellular deposition of fibrils. These are non-dissolvable polymers constructed out of subunits with a low-molecular weight, originating from a large diversity of proteins. Several types of amyloidosis exist; one can generally classify a primary form of amyloidosis (AL) and a secondary form (AA). AL amyloidosis is caused by deposition of immunoglobulin light chains. AA amyloidosis occurs with chronic diseases, especially those involving some form of an inflammatory process. Amyloidosis may affect various organs, but can also be limited to a single organ system. Signs and symptoms are, of course, highly dependent on the organ system involved.

### Cutaneous amyloidosis

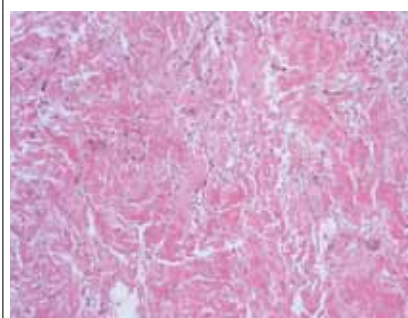
The skin may also be affected by amyloidosis. Several types of primary cutaneous amyloidosis have been described.

The three main forms of primary cutaneous amyloidosis are lichen (or papular) amyloidosis, macular amyloidosis and nodular amyloidosis.<sup>1</sup> In the first two forms amyloid fibrils are deposited in the papillary dermis. Nodular cutaneous amyloidosis is much rarer and may affect dermis, subcutis, but also vascular walls, and it may be attributed to some form of a localised plasma cell dyscrasia. Furthermore, the nodular type has a higher recurrence rate than the other forms. Progression from a local cutaneous form to systemic disease is rare, but in nodular cutaneous amyloidosis progression to a systemic disease has been reported in 7 to 50%.<sup>2,3</sup> Although there is no unanimous form of treatment, cutaneous amyloidosis is often treated by surgical excision. In case of nodular cutaneous amyloidosis, testing for systemic disease and extended follow-up appears appropriate, given the relatively high rate of progression to systemic amyloidosis.

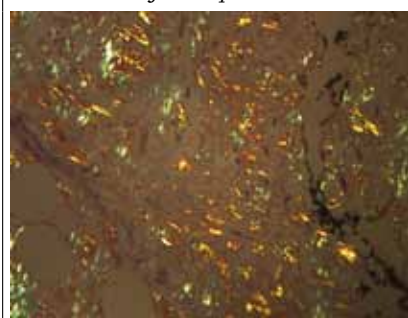
### Cutaneous amyloidosis and insulin

In our case it was remarkable that the location of both cutaneous amyloid tumours coincided with the sites at which our patient administered his insulin subcutaneously. The differential diagnosis of a tumour at such a location may include lipohypertrophy, a dermoid cyst or a lipoma, but should also include amyloidosis. As early as in 1983 the occurrence of amyloidosis at insulin injection sites was described in rats.<sup>4</sup> Although numbers are limited, a few diabetes patients have been described in literature, with cutaneous amyloidosis arising at the site of (repeated) subcutaneously administered insulin.<sup>4-11</sup> In several cases insulin (fragments) could be demonstrated in the amyloid tumours, as was the case in our patient. However, most case reports describe cutaneous amyloidosis in relation to non-human, i.e. porcine, insulin. The association with human (recombinant) insulin has, to our knowledge, been reported in even fewer case reports.<sup>6,9</sup> The mechanism of insulin-induced amyloidosis

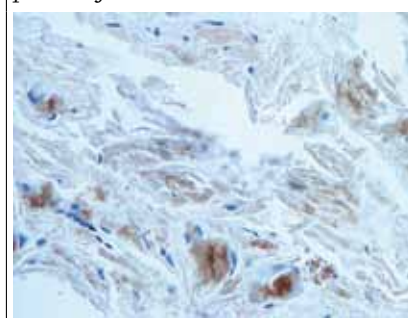
**Figure 1A.** Haematoxylin and eosin staining of the tumour. In the cutis distinct homogeneous eosinophilic areas with low cell density are present



**Figure 1B.** Area from figure 1A after staining with Congo red and using polarised light; the homogeneous areas are apple green, which is quite characteristic for amyloid



**Figure 1C.** Same area as in figure 1B after immunohistochemical staining with an insulin marker. The patchy brown areas are considered to be positive for insulin



is still unknown; it may be related to local accumulation of insulin, but further study is needed to clarify the pathophysiology of the association.<sup>9</sup>

## CONCLUSION

Cutaneous amyloidosis may be associated with local subcutaneous injections of insulin. Although initially only reported in patients using porcine insulin, the association also appears to apply to human (recombinant) insulin. Given the high prevalence of diabetes mellitus and insulin treatment, it is therefore advisable to also consider this diagnosis when finding tumours at sites of insulin injection.

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