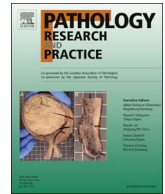




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Review Article

Current insight in the localized insulin-derived amyloidosis (LIDA): clinico-pathological characteristics and differential diagnosis

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ABSTRACT

Background: In diabetic patients, subcutaneous insulin injection may cause several types of injection site-related lesions, such as lipoatrophy, insulin-induced cutaneous lipohypertrophy (IICL), allergic reaction, and iatrogenic localized insulin-derived amyloidosis (LIDA). Among these complications, both IICL and LIDA present as tumor-like and slow growing lesions; and they may be confused with one another. The clinical implication and management of IICL and LIDA are different. LIDA causes poor blood glycemic controls due to inadequate absorption of the insulin. Thus, accurate diagnosis of the lesion is critical in diabetic patients.

Review of literature: LIDA is an extremely rare complication and often overlooked, it is managed by a surgical intervention. Whereas, IICL is a common side effect and can be managed by a non-surgical approach. Furthermore, in long-standing diabetics, patients may develop hypertrophic cardiomyopathy, proteinuria, peripheral, and autonomic neuropathy; these symptoms can be mistaken for a systemic amyloidosis. It is also necessary to distinguish LIDA from the systemic amyloidosis, which requires a more aggressive systemic therapy. LIDA should also be distinguished from primary cutaneous amyloidosis, with high risk of progression to a systemic amyloidosis. In this effort we reviewed 25 published manuscripts, including case reports and case series studies. We also summarized the literature and discussed differential diagnosis, including the approach to diagnose LIDA.

Conclusion: The identification of amyloid material and immunoreactivity with anti-insulin antibodies are key diagnostic features of LIDA. Although several clinical and animal studies were made in recent years, the lesion is still under-diagnosed and underreported. The clinical suspicion and knowledge of the lesion play a crucial role for the accurate diagnosis of LIDA. Surgical excision of the lesion can dramatically decrease insulin requirement and improve glycemic control.

1. Background

Iatrogenic localized insulin-derived amyloidosis (LIDA) is a nodular type of subcutaneous amyloidosis, which was first reported in 1983 [1]. It has been postulated that long-term, repeated, same site insulin injection is the most important predisposing factor for developing LIDA. A recent animal study has shown that the lesion is related to extracellular deposition of insoluble insulin, which forms amyloid fibrils in the injection sites [2–6]. The LIDA appears to be a 2–5 cm painless and firm subcutaneous nodule with an occasional color change of the overlying skin [3–6], and it can only be resolved by surgical resection.

In addition to type 1 diabetes, 30.8% of type 2 diabetes requires some form of insulin therapy in addition to their oral diabetic

medications, according to the 2011 report from the Center for Disease Control and Prevention. Theoretically, all type 1 diabetic patients and almost 30% of type 2 diabetics receiving insulin injections are at risk for developing LIDA. However, there is no data available regarding the actual prevalence of LIDA in the insulin-dependent diabetes. Among millions of insulin-dependent diabetic patients, LIDA is a seemingly rare complication of chronic insulin injections in a subset of diabetic patients [3–6], making it difficult to be accurately diagnosed.

LIDA may be confused with insulin-induced cutaneous lipohypertrophy (IICL) [5,7,8]. Similarly to LIDA, IICL also presents as a slow growing and painless cutaneous nodule [7,8]. However, the lesion develops around the site of insulin injections and has a softer texture than that of LIDA. The prevalence of the IICL is much higher in insulin-

Abbreviations: AA, amyloid A protein; AL, amyloid light-chain; CT, computerized tomography; H & E, hematoxylin and eosin; IHC, immunohistochemistry; LIDA, localized Insulin-derived amyloidosis; IICL, insulin-induced cutaneous lipohypertrophy; SAP, serum amyloid P; DM, diabetes mellitus; N/A, data is not available; Ab, antibody

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dependent patients. It is estimated that 50% of type 1 diabetic patients may develop lipohypertrophy over the course of their insulin therapy [12,7,8]. It has been related to the lipogenic and anabolic properties of the insulin [7,8].

In long-standing diabetics, patients may develop hypertrophic cardiomyopathy, proteinuria, peripheral, and autonomic neuropathy. These symptoms can be mistaken for systemic amyloidosis even in a LIDA patient without systemic amyloidosis. In contrast to systemic amyloidosis, which is characterized by the deposition of insoluble amyloid fibrils in multiple organs, LIDA is limited to the insulin injection site, and can be cured by resection of the lesion; whereas, the systemic amyloidosis requires a more aggressive therapy. In addition, the feature of subcutaneous deposition of insoluble insulin amyloid fibrils in LIDA should also be distinguished from primary cutaneous amyloidosis, which has a high risk of progression to a systemic amyloidosis [9,10].

Taken together, it is necessary to accurately diagnose LIDA from other lesions, particularly from IICL and systemic amyloidosis, because of different clinical managements among diverse diseases. Clinically, LIDA is still overlooked and undertreated. Herein, we have discussed clinical features, diagnosis and differential diagnosis of LIDA. We have also reviewed publications from the literature and summarized the current clinico-pathological knowledge of the entity. The purpose of our study is to update our knowledge of the lesion, to better understand the mechanism of disease, and to gain experience in making an accurate diagnosis.

2. Clinical findings of LIDA

We performed a literature search by using the following key words: insulin amyloidosis; cutaneous insulin injection and localized insulin-derived amyloidosis. We were able to find 18 individual case reports and a series of 7 cases. We summarized clinical findings of 25 published cases in Table 1.

2.1. Clinical features

Of 25 patients, 17 patients were male and 8 were female. The median age of the patients was 55 years. 54.5% (12 out of 22 cases) and 45.5% (10 out of 22 cases) were diagnosed as type 1 and type 2 diabetes, respectively. The type of diabetes was not reported in 3 cases from the original manuscript. Clinical information was available in 22 cases regarding the year of insulin injection and in 23 cases regarding the type of insulin injections. 86.4% case (19 out of 22 cases) had more than 10 years history and 22.7% cases (5 out of 22 cases) had more than 25 years of insulin injections. The average length of insulin injection was approximately 18 years, ranging from 4 to 47 years. Per reports, all cases were tested and negative for systemic amyloidosis.

The majority (80%, 20 out of 25) patients presented as a non-tender firm mass at the site of repeated insulin injections. The size of the lesion was smaller than 5 cm in 20 cases, however, 2 patients presented with masses larger than 5 cm [17,20], one patient didn't have any palpable mass at the time of diagnosis [19], and 3 cases were without information regarding the size of their lesions [16,24]. Only two patients had skin changes over the lesions, which were reported as hyperpigmentation consistent with acanthosis nigricans [13,21]. The locations of the lesions varied widely depending on the site of insulin injections, and the most common sites were abdominal wall, arms, and thighs.

LIDA caused an impairment of the insulin absorption at the injection site and an unpredictable release of insulin from nodules [3–5]. It led to poor glycemic control and other potential clinical complications. Among reported cases, 7 patients had to inject more than 50 units of insulin per day before the resection of the lesion; and in others, the average amount of injected insulin was more than 30 units per day. In a rare case, the usage of the insulin was as high as 450 units per day [26].

Even with such a high dosage of insulin, the average HbA1c among patients was 9.75%, which was above the recommended level of 6–7% for diabetic patients [6]. It was also reported that the daily insulin dose was increased more than 30 units in a short period of time, but without any improvement of the glycemic control in certain cases. From literature review, it was demonstrated that the insulin requirement was dramatically decreased from an average of 94–34 units/day after removal of the LIDA in 10 cases (P value = 0.02) [3,20,22,23]. The surgical excision of the lesion resulted in a dramatic decrease in the patient's insulin requirement and an improvement of glycemic control.

2.2. Pathological findings

A CT (computerized tomography) scan and/or ultrasound study revealed a circumscription dense subcutaneous lesion without increased vascularity or necrosis. On gross examination, the LIDA was well-demarcated lesion and surrounded by fibrous bands. Histological examination of the H & E (hematoxylin and eosin) sections revealed thick amorphous eosinophilic material (amyloid fibrils), and fibrous infiltration in the subcutaneous area without the involvement of the dermis. Scattered chronic inflammatory cells were seen in the lesion. The inflammatory cells consisted predominately of mature-appearing lymphocytes and plasma cells. Foreign body giant cell reactions were also identified in the lesion. No necrosis or vascular proliferation was seen (Fig. 1 our unpublished data). Although the presence of scattered acute and chronic inflammatory cells could be seen in the LIDA, it is a non-specific finding and could be seen in other forms of insulin injection site related lesions, such as allergic reactions.

The Congo-red stain of amyloid should be performed to confirm the diagnosis [2–5]. The stain of the subcutaneous amorphous and eosinophilic material revealed a diffusely and strongly staining pattern. The polarized microscope demonstrated that the amorphous material was a pink-red color under the light phase and birefringent green color under polarized phase (Fig. 2 our unpublished data), a characteristic birefringent color pattern of the amyloid.

Amyloid in LIDA is considered a secondary form (AA, amyloid A protein), rather than a primary form (AL, amyloid light-chain) of amyloidosis [14,15]. A polyclonal antibody against amyloid P component (SAP) and/or a monoclonal antibody against amyloid A could be used to identify the deposition of amyloid in the lesion [31]. In the majority of reported cases, the polyclonal antibody against SAP was used and stained diffusely for amyloid fibrils in lesions. However, the role of SAP in the pathogenesis of LIDA is still unknown.

The lesion was also immunoreactive with anti-insulin antibody. The area with amyloid deposition (Congo-red positive area) was diffusely and strongly positive for insulin immunostain. The lesion was negative for smooth muscle actin and S100 stains. No light-chain restriction was seen on either kappa and lambda stains.

2.3. Differential diagnosis

The main differential diagnosis of LIDA is with insulin injection associated lipohypertrophy, i.e. IICL [7,8]. We summarized the key features of differential diagnosis in Table 2.

The key diagnostic features of LIDA are the identification of localized amyloidosis and the immunoreactivity with anti-insulin antibody in the lesion, as well as lack of findings of systemic amyloidosis or involvement of other organs. The Congo-red stain of amyloid reveals a characteristic birefringent color pattern under polarized microscope [2–5].

IICL also presents as a soft cutaneous mass at the site of insulin injections and may be confused with LIDA [7,8]. Lipohypertrophy is caused by the lipogenic and anabolic properties of the insulin [7,8]. The prevalence of the IICL is much higher in insulin-dependent patients. It is estimated that 50% of type 1 diabetic patients may develop lipohypertrophy over the course of their insulin therapy [5,7,8,12].

Table 1
The summary of clinical information of LIDA cases.

Cases (Reference)	Age/Sex/Type of DM	Years of Insulin Injection	Lesion Size/Size/Texture	Positive reactivity to Abs	Daily Insulin Units Before/After Treatment	Type of Insulin	HbA1c Value (%) ^a
1- [11]	48/M/2	11	1 × 2 cm/para-umbilical/N/A	Compatible with AL	N/A	Mixtard	N/A
2- [3]	62/M/1	20	2-5 cm/N/A/firm	Anti-insulin	116/24	Lispro + Glargine	9
3- [3]	32/M/1	25	2-5 cm/N/A/firm	Anti-insulin	76/35	Aspart + Glargine	9.7
4- [3]	82/F/1	17	2-2-5 cm/N/A/firm	Anti-insulin	30/17	Lispro + Glargine	8.8
5- [3]	71/M/1	30	2-5 cm/N/A/firm	Anti-insulin	47/26	Lispro + Glargine	8.5
6- [3]	80/F/1	13	2-5 cm/N/A/firm	Anti-insulin	44/26	Aspart + NPH	10.2
7- [3]	68/M/1	18	2-5 cm/N/A/firm	Anti-insulin	33/26	Lispro + Glargine	9.5
8- [3]	58/M/2	17	2-5 cm/N/A/firm	Anti-insulin	52/34	Lispro + Glargine	9.6
9- [13]	59/M/2	4	4.5 cm/abdomen/firm ^b	N/A	N/A	Regular + NPH	7.6
10- [14]	54/M/N/A	N/A	3 cm/shoulder/firm	N/A	N/A	N/A	N/A
11- [15]	70/F/2	26	1.5 × 1 cm/abdomen/firm	Anti-insulin/Amyloid P (focal)	N/A	N/A	N/A
12- [16]	40/M/N/A	N/A	N/A/arm/N/A	Anti-insulin/Amyloid P	N/A	Humulin	N/A
13- [17]	34/M/1	17	7 cm/thigh/Firm	Anti-insulin	N/A	Humulin	8.3
14- [18]	25/M/1	11	4 cm/thighs/Firm	Anti-insulin/Amyloid P	N/A	Porcine + Mixtard	12.5
15- [19]	53/M/2	13	no mass	N/A	N/A	Recombinant human insulin	N/A
16- [20]	69/F/2	13	12 × 18 cm/abdomen/soft	N/A	132/42	Human premixed + NPH	7.6
17- [21]	54/M/2	5	5 × 4 cm/paraumbilical/firm ^b	N/A	N/A	Recombinant human insulin	15.5
18- [22]	62/M/1	20	3-4 cm/abdomen/firm/	Anti-insulin	116/66	Lispro + Glargine	8.6
19- [23]	59/M/1	47	2 × 3 cm/abdomen/firm	Anti-insulin/Amyloid P	290/45	NPH + Lispro	10.9
20- [24]	33/M/1	23	5 × 2.5 cm/forearm/firm	Anti-insulin/Amyloid P	N/A	Regular + Aspart + NPH	N/A
21- [24]	78/F/2	4	N/A/abdomen/N/A	Anti-insulin/Amyloid P	N/A	Mixtard	N/A
22- [24]	42/F/1	27	N/A	Anti-insulin/Amyloid P	N/A	Regular + Aspart + NPH	N/A
23- [24]	38/M/1	N/A	5 × 5 cm/arm/N/A	Anti-insulin/Amyloid P	N/A	NPH + Lispro	N/A
24- [25]	60/F/NA	18	4.5 × 3.5 × 2 cm/abdomen/soft	Anti-insulin	N/A	Human insulin + Lispro + Aspart	10
25- [26]	N/A/F/2	14	3 nodules, 5.5 × 3.5 and 2.5 × 2.5 and 1.7 cm/abdomen/firm	N/A	450/NA	Concentrated human insulin	N/A

DM: Diabetes Mellitus.

N/A: Data is not available.

AL: Amyloid light-chain.

Ab: Antibody.

^a HbA1c value at the time of admission.

^b Coexistent with acanthosis nigricans.

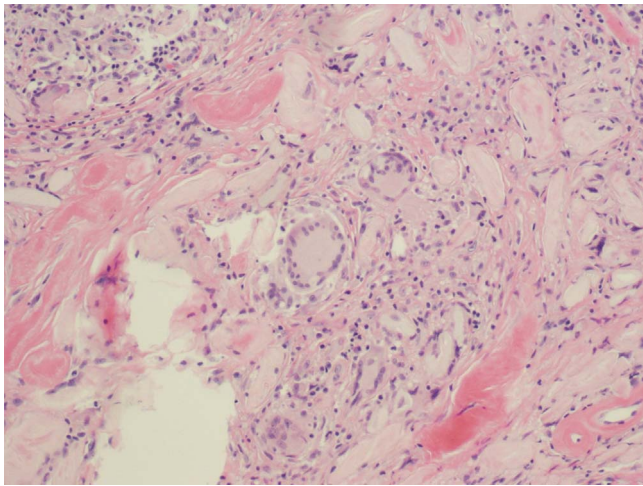


Fig. 1. Histological examination of the lesion. H & E sections revealed amorphous eosinophilic material and fibrous band in the subcutaneous area without the involvement of the dermis. Scattered chronic inflammatory cells and foreign body giant cell reactions were also seen. No necrosis or vascular proliferation was seen (20X magnification).

Morphologically, lipohypertrophy reveals a lobular proliferation of adipose tissue with focal fibrosis and edematous changes around the insulin injection site. In the lesion, all adipocytes are mature and without any cytological atypia. The lesion can be resolved by cessation of insulin injection, and usually do not require a surgical intervention.

Interestingly, lipohypertrophy and LIDA can co-exist in the same lesion. For instance, a patient was found to have two masses in the thigh, one was diagnosed as LIDA and the other was diagnosed as lipohypertrophy (18). A recent study has shown that daily injection of insulin for 21 days was associated with the formation of LIDA in mice [2]. Interestingly, Sudan black staining also identified the presence of hyperplastic lipocytes in the lesion. These findings are important because co-existence of lipohypertrophy and localized insulin-derived amyloidosis was reported in human LIDA cases [18]. Therefore, a suspicious lesion should be evaluated for both pathologies.

Although the systemic amyloidosis should be considered in the differential diagnosis, lack of systemic manifestations and negative immunoreactivity with anti-insulin antibody in the lesion can help with the differential diagnosis of the LIDA. The finding of cutaneous amyloid and inflammatory cells are non-specific and can be seen in nodular type of primary cutaneous amyloidosis and/or systemic amyloidosis. Nodular cutaneous amyloidosis is a rarer disease with amyloid depositions not only in the subcutaneous area, but also in the dermis and vascular walls. The lesion is caused by a localized plasma cell dyscrasia [27]. In nodular type of primary cutaneous amyloidosis, the lesion does not have the immunoreactivity with anti-insulin antibody. It also has a higher risk of relapse and progression from localized form to systemic

amyloidosis [10].

Finally, the mechanism of development of LIDA has been related to deposition of insoluble insulin fibrils with the cross-linkage of the β structure [2]. LIDA is a painless lesion, and as a result, patients have a tendency to continue insulin-injection at the same site to avoid stick pain, which may also play a potential role for the facilitation of formation of LIDA [15]. It has been demonstrated that insulin-derived amyloidosis is formed through a self-assembled process [29]. The formation of the LIDA has also been related to a higher concentration C-peptide of the insulin at the injection site [13,30]. Further studies are still needed for better understand the molecular mechanism of the lesion.

3. Conclusion

LIDA is a rare and often overlooked cutaneous lesion. It is caused by the insulin injection and can be cured by surgical resection of the lesion. The identification of amyloid material and immunoreactivity with anti-insulin antibody are key diagnostic features of the lesion. Although several clinical and animal studies are made in recent years, the lesion is still under-diagnosed and underreported. The clinical suspicion and knowledge of the lesion play a crucial role for the accurate diagnosis of LIDA. Surgical excision of the lesion can dramatically decrease the patient's insulin requirement and improve glycemic control.

Declarations

Ethics approval and consent to participate

The ethical approval and documentation for a review manuscript was waived with approval of the Institutional Review Board at the Johns Hopkins Medical Institutions.

Availability of data and material

There is no supporting data available.

Competing interests

The authors declare that they have any competing interests.

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8. Authors' contributions

AMA: literature review, data analysis and drafting the manuscript, LO: review pathology and data analysis, AEM: drafting the manuscript,

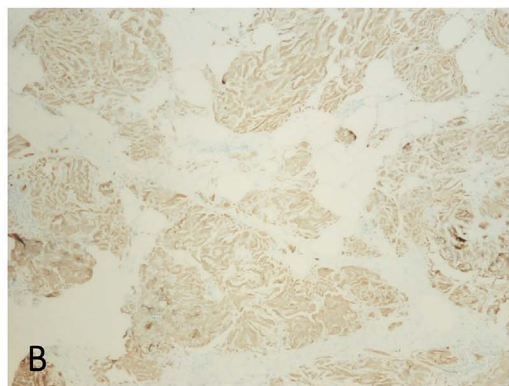
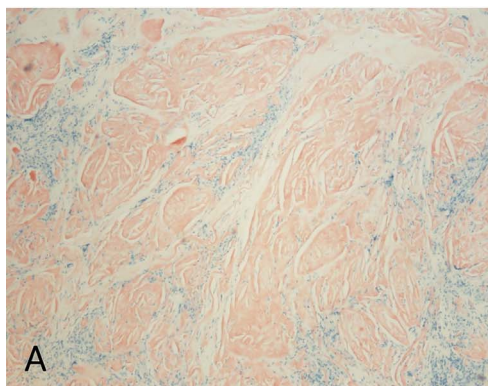


Fig. 2. Congo-red staining pattern. A Congo-red stain demonstrated diffusely and strongly pink-red color (4X magnification). B a immuostain of insulin demonstrated diffusely positivity in the lesion (4X magnification).

Table 2

Characteristics of Localized insulin-derived amyloidosis (LIDA) and insulin-induced cutaneous lipohypertrophy (IICL).

Characteristics	Lipohypertrophy (IICL)	Localized Amyloidosis (LIDA)
Location	Around the insulin injection site	In the insulin injection site
Average size	Variable	Usually less than 5 cm
Nodule characteristics	Soft, Lobular subcutaneous painless mass	Firm, circumscriptive subcutaneous painless mass
CT-scan Findings	Lobulated, focal subcutaneous fatty lesion, without increased vascularity	Well-circumscribed, focal subcutaneous dense lesion, without increased vascularity
Histological Findings	Mature adipocytes containing lipid droplets, focal fibrosis and edematous changes.	Eosinophilia material, subcutaneous fibrosis, infiltration of scattered inflammatory cells.
Amyloid stains (Congo-red and/or IHC stains)	Negative	Positive
Immunoreactivity with anti-insulin antibody	Negative	Positive
Clinical management	Rotation of insulin injection sites	Surgical resection

and QKL: study design, critical revision of the manuscript. All authors read and approved the final manuscript.

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