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Tissue Reactions to Injectable Biomaterials: Histopathological Features and Mechanisms; As Article Review

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Abstract

In aesthetic medicine, tissue engineering, drug delivery and reconstructive surgery, the use of injectable biomaterials is key. After injection, these materials undergo interactions with the extracellular environment that trigger host responses that are dependent on their chemical composition, physical properties, degradation, injection site, and local tissue conditions. The reactions vary from transient inflammation and tissue remodeling through to persistent foreign-body reactions, granulomatous inflammation and fibrosis. This is a narrative review of the pathological changes and biological processes involved in tissue reactions to injected biomaterials. Special emphasis is placed on neutrophil recruitment, macrophage activation, formation of foreign body giant cells, involvement of lymphocytes, activation of fibroblasts, deposition of extracellular matrix and fibrous encapsulation. Hyaluronic acid (HA), calcium hydroxyapatite (CaHA), poly-L-lactic acid (PLLA), polymethyl methacrylate (PMMA), silicone, and some hydrogels are reviewed. Evidence from human filler biopsies and mechanistic evidence from animal models, in-vitro experiments, scaffolds and surgically implanted devices are differentiated. The histopathological diagnosis must be correlated with the clinical data and with the history of the injected material as there may be overlapping patterns in sterile inflammation, infection and other diseases.

Keywords

Injectable Biomaterials;
Foreign Body Reaction;
Histopathology;
Macrophages;
Foreign Body Giant Cells;
Granulomatous Inflammation;
Fibrosis;
Biocompatibility.

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1. Introduction

Biomaterials are recognized as a valuable resource in contemporary medicine for a wide range of applications including tissue augmentation, tissue reconstruction and regeneration, and localised therapeutic delivery. They can be biodegradable fillers, non-biodegradable injectable substances or matrices that facilitate tissue repair depending on their composition and the purpose for which they are used. Their clinical effects are accompanied by biological responses that impact degradation, tissue integration, inflammation and long-term performance.

Biomaterials will elicit a host response that is not a single stereotyped inflammatory event. Proteins in the local biological environment adsorb to the surface of the material immediately after the injection and affect the recognition and adhesion of cells. Typically, early response includes neutrophils and monocyte-derived macrophages; chronic materials are usually accompanied by foreign body giant cells, chronic inflammatory infiltrates, and fibrous tissue which cover or intermingle with the material [1,2]. Mechanisms can be explained from the evidence and implanted devices, but not regarding the frequency or significance of the same responses in dermal fillers.

Macrophages play a crucial role in the foreign body response by virtue of their phagocytic, inflammatory, tissue remodeling, and even, in certain situations, fusogenic properties, which culminate in the formation of the foreign body giant cell. Giant cells can contact materials which are not easily ingested by individual macrophages. The interaction of macrophages, lymphocytes, fibroblasts, and extracellular-matrix components can influence the persistence and degradation of materials, their vascularization, and the fibrotic encapsulation [1-4].

Histologic responses of tissues to injectable biomaterials are heterogeneous. Macrophage rich infiltrates, multinucleated giant cells, granulomatous inflammation, collagen deposition, cyst like spaces, and varying amounts of residual material can be found. These findings are none individually pinpoint a particular complication or commercial product. The injected substance, interval from the injection to the biopsy, anatomical location, effects of tissue processing and the presence of infection or other inflammatory disorder should be taken into consideration in interpretation [5,6].

Foreign body reactions do not always have a negative effect. Tissue integration can be accompanied by a controlled inflammatory response and remodeling, or an excessive and prolonged inflammatory response or fibrosis may lead to palpable nodules, tissue distortion or dysfunction. The histopathological patterns and the cellular and molecular interactions, along with the material-specific evidence, limitations in diagnosis and implications for biomaterial design are described.

2. Review Methodology

The article was done in the critical narrative method, not systematic review or meta-analysis. Literature searches were conducted with the help of the databases PubMed and official websites of the scientific journals and publishers of interest. The keywords and terms used in the search were: “injectable biomaterial,” “dermal filler,” “histopathology,” “biopsy,” “foreign body reaction,” “foreign body giant cell,” “granuloma,” “hyaluronic acid,” “calcium hydroxyapatite,” “poly-L-lactic acid,” “polymethyl methacrylate,” “silicone” and “fibrosis”. Searches were performed for mechanistic reviews, human clinicopathological studies, case series and material-specific investigations of tissue morphology and pathogenesis of biomaterial associated reactions. Because the search was not exhaustive, there were no formal study-selection counts, systematic risk-of-bias assessment, or PRISMA flow diagram of the search process.

Histopathological descriptions, biopsy results in humans, clinical responses of tissues to certain materials, and descriptions of mechanisms leading to activation of the macrophages, formation of foreign body giant cells, granulomatous inflammation and fibrosis were given priority. If possible, bibliographic data were corroborated with the corresponding web pages of the publishers and PubMed data. Existing data was assessed with respect to study design, methodological limitations and clinical relevance and human studies regarding the development of tissue reactions to fillers were seen as particularly relevant to the understanding of the histopathological reactions to injectable fillers. Basic background data on the properties and characteristics of the various types of injectable fillers was determined from Reference [16].

When discussing animal studies, in vitro research, and surgical implants or experimental scaffolds, the focus was mostly on elucidating potential biological mechanisms.In the context of animal studies, in vitro studies and surgical implants/experimental scaffolds, the focus was on elucidating potential biological mechanisms. Incidence rates and/or risks of complications were not calculated using case reports or small case series. Results from permanent implants were drawn with a healthy degree of scepticism as differences in implant geometry, tissue distribution, degradations rates and mechanical environment could restrict the extrapolation of the results to injectable fillers.

Five main themes were discussed: (1) acute and chronic inflammatory response; (2) activation of macrophages and foreign body giant-cell formation; (3) development and fibrosclerosis of a granuloma; (4) material-specific features of the histopathological response; and (5) diagnostic difficulties and implications for biomaterial safety. The probability of review was a narrative type and the evidence was heterogeneous so neither pooled effect estimates nor quantitative meta-analysis was conducted.

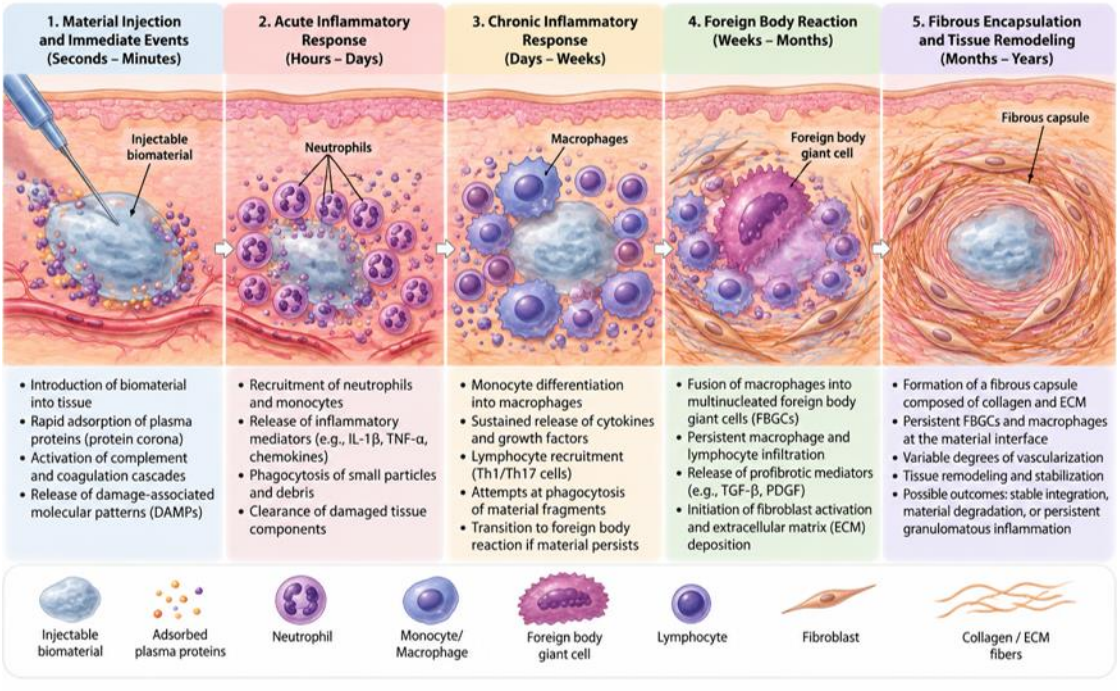


Figure 1. Conceptual sequence of the foreign body response.

3. Biological Basis of Tissue Reactions

3.1. Initial tissue injury and protein adsorption

Local damage to tissues, including damage to small blood vessels and to the extracellular matrix occurs after injection. This leads to a wound response with haemostasis, provisional matrix formation and recruitment of inflammatory cells. Proteins adsorb to the surface of materials very quickly and, when done, make an interfacial layer which can affect cell adhesion and host recognition.

Biological identity of a material is not only based on chemical composition. Other factors that can modify the interactions between materials and tissue, and the foreign body response, are adsorbed proteins, local fluid environment, surface properties and degradation products, and the tissue environment [1,2,7]. Many of the mechanistic findings are from the general biomaterials or implant models and should not be extrapolated to any single injectable filler.

3.2. Acute and chronic inflammation

In the acute inflammation, neutrophils are recruited, there are vascular changes, and inflammatory mediators are released. Monocytes then can enter the affected tissue and transform into macrophages. These reactions are variable in severity and duration depending upon the nature of the tissue injury, persistence of the material, local factors and infection or lack of infection [1,2,14,15].

The inflammation can decrease when tissue repair is taking place and the material is breaking down or eliminated. However, the presence of chronic inflammatory infiltrates can be a sign of ongoing immune activation or microbial infection, or chronic tissue damage. The presence of chronic inflammation is not, per se, indicative of a complication; this depends on the pattern, clinical presentation and impact of the inflammation on tissue function.

3.3. Macrophage responses and foreign body giant cells

Macrophages are involved in the functions of phagocytosis, inflammatory signaling, tissue repair and material degradation. Macrophages can attach to the surface of a material that is too big to be ingested by one cell and fuse into a multinucleated foreign body giant cell.

The formation of foreign body giant cells requires adhesion of the macrophages, reorganization of their cytoskeleton, migration and fusion-associated signaling pathways. These processes could be affected by cytokines, cell-surface molecules and physical and chemical properties of materials [3,4,8]. Proposed mechanisms are provided by the evidence from the implant models, but do not establish that the same mechanisms are as equally significant and as likely to occur in all types of injectables.

Foreign body giant cell can be present around foreign body in tissues and may be involved in extracellular degradation and local remodeling. Giant cells do not necessarily indicate clinically significant disease: The presence of giant cells alone does not signify a clinically significant disease, as these cells could be a component of a foreign body reaction without a clinically symptomatic problem. The four aspects which need to be taken into consideration when interpreting is the material, distribution of the reaction, accompanying tissue injury, and clinical presentation.

3.4. Adaptive immunity and granulocytes

While innate immune cells are almost always involved in the initial response to biomaterials, adaptive immune cells can also be involved. Macrophages also communicate with T lymphocytes and other cells, affecting their activation, their ability to sustain inflammation and to drive fibrotic remodeling. There are experimental models and materials that to a

certain extent involve adaptive immune mechanisms [9].

The eosinophils and basophils can modulate or control the immune response, or even remodel tissues in some circumstances involving biomaterials, while neutrophils are mostly involved in acute inflammation. The roles are dependent on the material and the study model and cannot be generalized for all injectable products [10].

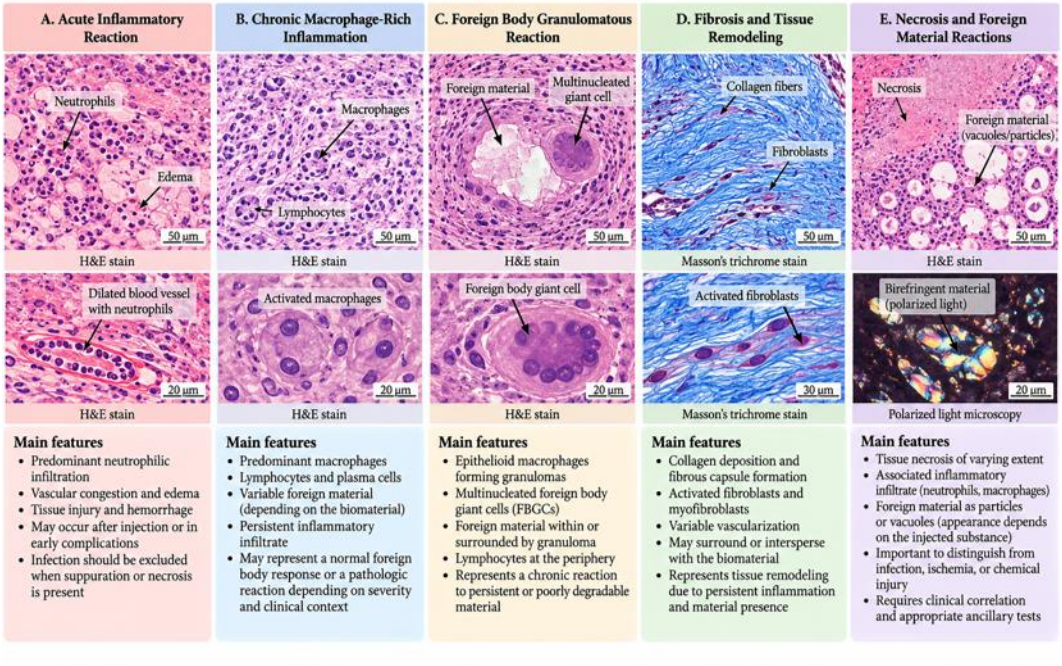


Figure 2. Main histopathological reaction patterns.

4. Histopathological Features

4.1. Acute inflammatory pattern

Neutrophils, interstitial oedema, vascular congestion and tissue injury are among the histological changes which may be acute. They are more severe if they are injected and biopsied in a shorter time and if they are subjected to a more extensive local injury. Acute inflammation with an infiltrate and necrosis or an abscess is associated with infection; a sterile acute inflammation doesn't. Clinical evaluation and proper microbiological exams might be necessary to differentiate these possibilities.

4.2. Chronic macrophage-rich inflammation

Macrophages, lymphocytes, plasma cells and sometimes a number of multinucleated giant cells are found in chronic reactions. It can be found extracellularly either as particles or as a lack of material (vacuole-like) following the processing of the tissue. Consideration of the suspected submission material and processing method of the product is necessary as some materials may be altered, dissolved or lost during preparation that may result in an incomplete representation of the product being injected.

4.3. Foreign body granulomas

Foreign body granulomatous inflammation is characterized by the presence of collections of macrophages, epithelioid macrophages and/or multinucleated giant cells either in association with or surrounding foreign material. At the periphery,

lymphocytes and fibrosis can be found. Granulomas are not specific for the materials that are injected, and can be seen with infection, systemic inflammatory disease or other foreign substances. When necessary, clinical history, morphology, special stains and microbiological testing should be combined to form a differential diagnosis [5,6].

4.4. Fibrosis and tissue remodeling.

Fibrosis is caused by abnormal (or chronic) buildup of extracellular-matrix components such as collagen. Activated fibroblasts and myofibroblasts make and remodel matrix; mediators produced by macrophages and other cells can modulate the activity of the fibroblasts. Persistent material can lead to the formation of a fibrous capsule, the effects of which are dependent on its thickness, organization, location and function. Fibrosis is not always beneficial or detrimental, as it can hinder function in some situations, but not in others, therefore fibrosis alone should not be deemed as always good or bad [7,11].

4.5. Necrosis and other tissue injury

Necrosis does not have to be a part of the reaction to biomaterials. May result from any of the following: severe local injury, impaired perfusion, infection, chemical injury or other complication. When determining causation of an injection, history of injection, anatomical distribution, clinical course and evidence of ischemia is relevant for Injectable Fillers. This does not prove that the injected material was to blame.

5. Material-Specific Tissue Reactions

5.1. Hyaluronic acid

Injectable fillers are commonly made out of a naturally occurring glycosaminoglycan called hyaluronic acid (HA). There are variations in tissue response depending on molecular properties, cross-linking, formulation, degradation, injection technique and site. Histological features may consist of spaces containing material, variable macrophage infiltration and occasionally multinucleated foreign body giant cells. Delayed nodules are not necessarily foreign body granulomas, but can be sterile inflammation or infection, or other reactions of the local tissues [5,6,12].

5.2. Calcium hydroxylapatite

Fillers made of calcium hydroxyapatite (CaHA) are made up of mineral particles that are dispersed in the carrier. The tissue responses reported are those associated with the presence of the particle and are characterized by inflammation and collagen remodeling. Histological evaluation should be used to clarify the difference between material-associated remodeling and excessive inflammatory response and take into account the location of the affected area, the presence of macrophages, giant cells and collagen deposits, and the clinical presentation. Comparative human evidence (CaHA vs PLLA) is applicable only to the present study formulation and treatment site and biopsy timing and should not be extrapolated to other products [22].

5.3. Poly-L-lactic acid

Poly-L-lactic acid (PLLA) is a biodegradable polymer that has been used to stimulate tissue augmentation, by breaking down the polymer and stimulating collagen production. Histologic observations reported include an amount of variable collagen deposits and macrophages, and multinucleated giant cells around particles. The results of these vary with particle properties and distribution, rates of degradation, injection site, time to biopsy, and host response. In some cases, persistent inflammation and/or palpable nodules can occur, but there is no consistent response among different formulations [13,22].

5.4. Polymethyl methacrylate

Polymethyl methacrylate (PMMA) is a long-lasting manmade material. Macrophages, multinucleated

foreign body giant cells and fibrous tissue may be found with microspheres in tissue. Dermal-filler injection has been associated with granulomatous reactions, with varying outcomes; and differential diagnosis is required to diagnose them [5,13]. A persistent nodule may be helped to be characterized by histopathology, but the results should be interpreted in conjunction with the history of the injection and other possible causes [5,21,24].

5.5. Silicone

The tissue reactions following silicone are dependent upon the volume of the injection, distribution of silicone, physical form of silicone and history of injection. Histological changes include vacuolated spaces, macrophages, multinucleated giant cells and different fibrosis. If a suitable clinical situation exists, silicone-associated granulomatous inflammation can be considered. But vacuolated areas in processed tissue are not definitive for silicone unless the tissue pattern is evaluated in conjunction with the clinical history and the correct tissue evaluation [5].

5.6. Natural and synthetic hydrogels

The application of the hydrogels are in tissue engineering, regenerative medicine, and controlled-delivery system. They respond biologically according to their polymer chemistry, cross-linking, swelling, mechanical properties, degradation and protein and cellular interactions. There are some formulations that break down and others that offer longer lasting matrices. Mechanisms of macrophage recruitment and fibrosis can be studied with experimental scaffolds and implanted-hydrogel studies that can inform, but cannot be directly extrapolated to an injectable product without product specific evidence [1,14,15].

6. Comparative Histopathological Interpretation

Table 1. Histopathological Features and Potential Clinical Interpretation of Tissue Reactions to Injectable Biomaterials.

Feature	Potential interpretation	Important limitation
Neutrophils	Acute inflammation; possible infection	Not specific for infection
Macrophages	Material clearance, chronic inflammation, or remodeling	May occur in expected tissue responses
Multinucleated giant cells	Foreign body response	Do not independently establish a complication
Granulomatous inflammation	Persistent immune reaction to material or another cause	Requires differential diagnosis
Collagen deposition	Tissue repair or fibrosis	Clinical significance depends on extent and location
Necrosis	Severe tissue injury, ischemia, infection, or another process	The cause cannot be assigned from necrosis alone
Vacuolated spaces	Possible residual or processed-out material	Material identification may require additional evidence

Any comparison to a clinical end point needs to be able to separate tissue integration from an adverse reaction. Staining and morphology are not individually diagnostic; mucin-like staining may be of assistance in the identification of HA deposits; in the right circumstances, Alcian blue or colloidal iron may be of assistance. In a small, comparative human study, PLLA and CaHA were associated with different forms of cellular response and collagen remodeling in the arms treated; these results cannot be extrapolated from one product to another, as the study was designed, the preparations used, and the timing of the biopsies differ [22]. Long-term granulomatous inflammation and fibrosis may be linked with persistent materials like PMMA and silicone, although this is not specific. The microscopic appearance can change due to processing artefacts, infection, amount of material and time elapsed. The observed pattern should be described and interpreted, using clinical information; a commercial product cannot be identified by morphology alone [5,6,17,19,22-26].

A single finding; do not use for a histopathological diagnosis. The distribution and nature of the inflammatory infiltrate, associated with recognizable material, tissue damage, processing, clinical history and time since injection should be analyzed as a whole.

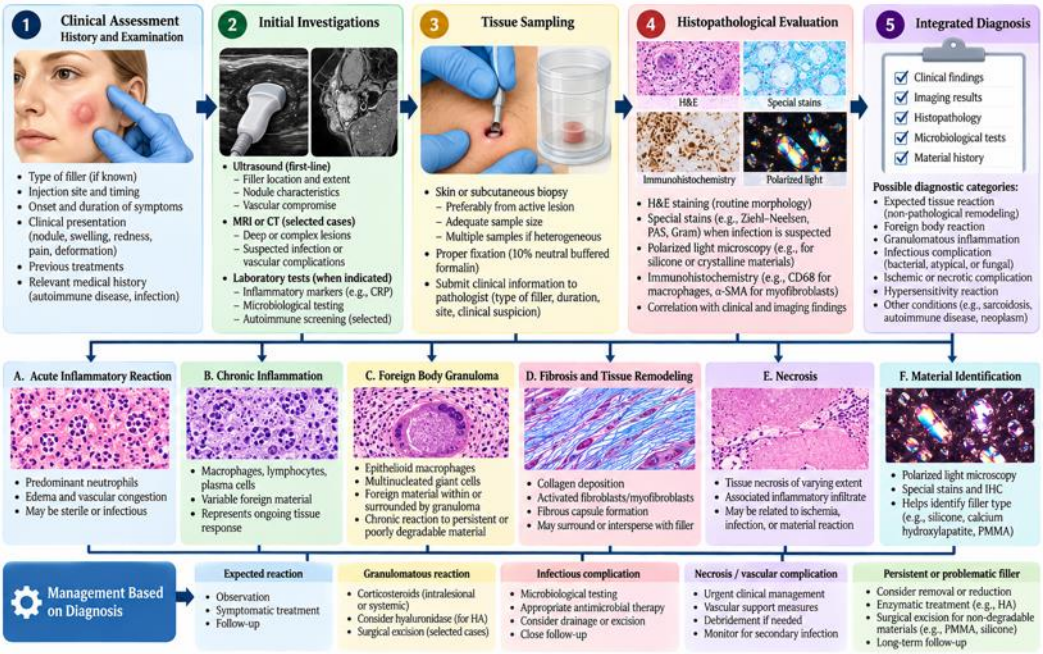


Figure 3. Practical diagnostic workflow for suspected filler-related reactions.

Table 2. Comparative Histopathological Features and Tissue Responses Associated with Selected Injectable Biomaterials.

Material class	**Typical material appearance / location**	**Possible tissue response**	**Interpretive caution**
Hyaluronic acid (HA)	Mucin-like / basophilic extracellular deposits	Macrophages; occasional granulomatous inflammation; variable fibrosis	Alcian blue/colloidal iron may support identification; morphology alone is not definitive
Calcium hydroxyapatite (CaHA)	Particulate mineral material in carrier	Particle-centred macrophages/giant cells; collagen remodeling	Inflammation varies with formulation, depth, and time
Poly-L-lactic acid (PLLA)	Biodegradable polymer particles	Macrophages/giant cells; collagen and elastic-fibre remodeling	Degradation stage and particle distribution affect appearance
PMMA	Persistent microspheres	Chronic particle-associated macrophages/giant cells; fibrosis or granuloma	Long persistence does not mean every deposit is clinically adverse
Silicone	Vacuolated spaces / droplets or material clefts	Granulomatous inflammation, giant cells, migration, fibrosis	Processing and injected silicone form can alter the microscopic pattern
Hydrogels	Variable gel spaces or polymer-rich regions	Response depends on chemistry, cross-linking, degradation, and mechanics	Broad category; avoid assuming one histological signature

7. Diagnostic Approach and Clinical Implications

7.1. Histopathological assessment

- Document the clinical history, including the type of injected material, injection site, timing, and onset of symptoms.
- Review the inflammatory infiltrate, cellular composition, distribution and relationship to the material.
- Evaluate for gross multinucleated giant cells, granulomas, fibrosis, necrosis and other pertinent changes in the tissues.
- If infection or some other special cause is suspected, then special stains and microbiological testing should be considered.
- Relate the microscopic data to the clinical picture and as necessary, imaging or other diagnostic studies.

7.2. Distinguishing sterile reactions from infection

Sterile inflammatory reactions and infectious complications may have the same clinical and histological features. If an inflammatory nodule is delayed, it can be due to foreign body response, infection or a combination of both. A lack of microorganisms on routine histology and a lack of a special stain doesn't rule out infection and giant cells are non-specific. If infection is still a possibility, the clinical situation should be considered along with appropriate special stains, microbiological testing of tissue culture or other microbiological techniques should be considered.

7.3. Implications for biomaterial design

Acute toxicity is not the only parameter to evaluate for biocompatibility. Other factors of interest are chronic inflammation, degradation products, tissue integration, fibrotic encapsulation and long-term functional performance. Strategies that could be considered for design include controlling particle sizes and distributions, changing the surface chemistry, altering degradation rates, and optimizing mechanical properties of the particles for the intended tissue. The latter approaches need to be tested experimentally as altering one inflammatory pathway can also impact on the degradation, integration or other biological performance aspects [1,3,7].

8. Discussion

8.1. Relationship between material properties and tissue responses

There are indications in the literature that a tissue reaction to injectable biomaterials is a function of the tissue environment and the properties of the material. The chemical components are relevant, but not in and by themselves, in terms of the intensity or length of the response. Other factors like geometry, surface properties, rate of degradation, mechanical behavior and local tissue properties can also affect the inflammation and remodeling [1,3,4]. When applied to injectable fillers, the evidence from the implanted devices is still indirect and provides a mechanism that can be used to understand the process. The concept of biocompatibility is also summarized in other review papers [27,28,30].

There might be different reaction patterns when using biodegradable and persistent materials. Biodegradable materials can break down chemically or enzymatically which may result in the liberation of intermediates during the process and alteration in their properties over time. Some materials do not get absorbed and can interact with macrophages and other cells at the injection site for a prolonged period. The conditions for clinical success with biodegradability or persistence are not solely dependent upon the formulation or site, dose or host reaction and follow-up.

8.2. Macrophage heterogeneity and foreign body reactions

Macrophages have been categorized in a rather simplified inflammatory/reparative manner. While this is a convenient theoretical concept it is not applicable in the real world of the living tissues, where macrophage states are more complex and do not fall into a simple dichotomy. Macrophages can play a role in inflammatory signaling, degradation of materials, angiogenesis, matrix remodeling and fibrosis. Local cytokines, materials properties and interactions with immune and stromal cells [3, 4, 9] all affect their activity. Some mechanistic context is provided by reviews of implant associated immune responses [29].

When foreign material persists for a long time, foreign body giant cells may develop as a result of the fusion of macrophages. These cells at the material–tissue interface could be involved in both material degradation and/or local remodeling. They are biologically significant based on their context and activity, the material involved, any inflammatory or

tissue injury and clinical findings; their presence alone is not a sign of a complication.

8.3. Fibrosis: Adverse Outcome or Component of Tissue Integration?

Collagen deposition takes place in the wound healing process, tissue integration and some chronic foreign body reactions. Failure does not necessarily equal fibrous capsule, as its effects are related to thickness, organization, vascularity, mechanical properties and location. In some instances, extensive encapsulation can inhibit functionality of a material and in others; the process of matrix deposition can stabilize a material or be used to augment it. The collagen content is not only considered but also the architecture of tissues and the functional consequences of the collagen [7,11].

8.4. Diagnostic limitations

Some material-associated reactions can be hard to diagnose as there are different patterns that can be found in similar processes. Macrophages, multinucleated giant cells, lymphocytes and fibrosis are not unique to a particular material or complication and the tissue processing may change or remove the original material. The use of the history, suspected product, imaging findings, timing of injection and evidence for alternate diagnoses (infection) should form the basis of interpretation. There is also a variety of published studies, which differ in terms of formulation, injection site, indication, follow up, biopsy sampling, and histological methods. Small case series do not provide a reliable estimate of the rate of complications, and the rate of complications from experimental implants should not be inferred from the findings of the implant without supporting evidence [5,6,17–20].

8.5. Research gaps and future directions

- Standardization of the histopathological description of foreign body reaction, granuloma and material-associated fibrosis should be emphasized to make the description of the reactions more comparable.
- Longitudinal studies with good follow-up should be performed to establish a relationship between early inflammatory patterns and delayed nodules, granulomatous reactions or fibrosis.
- The chemistry of the materials, particle size and distribution, degradation characteristics and conditions at the point of injection all should be evaluated separately, but may interact with one another in future studies.
- Macrophages, lymphocytes and fibroblasts may be distinguished and characterized by location and activity, using multiplex immunohistochemistry and other advanced analytical techniques, in material-associated reactions.
- Mechanistic findings should be related to clinically relevant outcomes and not just be read in the light of laboratory markers.
- When infection is suspected, the injected product, anatomical site, time of onset of symptoms, diagnostic procedures and microbiological findings should always be recorded for any reports of complications.

8.6. Strength and limitations of the evidence

Mechanistic reviews, human biopsy data, limited comparative studies and systematic reviews of select complications comprise the evidence base. One of the advantages of this literature is that the opportunity is presented to understand the pathological changes observed in relation to accepted mechanisms of the foreign body reaction. Some of the limitations are that there is a lack of uniformity of terms used, incomplete reporting of the injected product and time to onset, inconsistent timing of biopsies, small clinical samples, and potential publication bias for atypical or severe

cases. The frequency and clinical importance of reactions to any injected filler can only be determined by studies of implanted devices. This article employs a narrative search, which is not used in the formal, score-based, risk-of-bias assessment of the literature and lacks quantitative synthesis of the results, so causal inference and direct product-to-product risk comparisons are not feasible [1,5,14,15,17,19,22,23].

9. Conclusion

Tissue Response to Injectable Biomaterials is a process involving interactions of the properties of the biomaterial, local tissue microenvironment and host immune system. Histopathological finding include acute inflammatory infiltrates, macrophage accumulation, multinucleated foreign body giant cells, granulomatous inflammation and fibrosis. These findings are related to overlapping processes of inflammation, persistence of material, degradation and remodeling of tissues rather than one united pathological reaction.

Macrophages and multinucleated foreign body giant cells are involved in responses at material surfaces, and can modulate the activity of other cells such as fibroblasts and deposition of extracellular matrix that can affect material degradation. Macrophages, giant cells and collagen deposition are not however diagnostic individual entities of a complication. It should relate the histology to the injected substance, the clinical history, the location of the tissue, the time from injection, and any other possible diagnoses, such as infection.

The difference between materials is important, but not enough to be able to predict a particular clinical outcome. Standardized histopathological criteria, detailed cellular characterization and well documented clinical follow-up are required for further studies and clarification of delayed reactions and fibrosis. It can enhance pathological diagnosis, the safety evaluation of biomaterials and the design of injectable biomaterials with long term performance and tissue integration.

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