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Secondary minimal change disease

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Abstract

The great majority of patients identified as having a 'minimal change lesion' accompanying the nephrotic syndrome have a primary or 'idiopathic' disorder. Nevertheless, it is quite apparent that a similar or identical lesion can appear consequent to a growing number of underlying diseases; it is then known as 'secondary minimal change disease'. The predisposing conditions include neoplastic diseases, toxic or allergic reactions to drugs, infections, auto-immune disorders and other miscellaneous entities. These disorders are reviewed and catalogued in this contribution.

Keywords: drugs; infections; minimal change; minimal change disease; neoplasia; nephropathy; secondary nephrotic syndrome

Introduction

The term minimal change disease (MCD) is representative of 'hybrid' nomenclature in that it describes a morphological finding, which also connotes a clinical phenotype [1]. Although the pathogenesis of this disorder remains obscure, it is very likely that a systemic disturbance is responsible for the characteristic 'leakiness' of the glomerular capillaries and the diffuse effacement of epithelial cell foot processes. Delineation of primary and secondary forms of MCD may provide an artificial separation of disorders, which have a common underlying pathogenetic basis. Primary or 'idiopathic' MCD is characterized by perturbations in glomerular permselectivity (chiefly charge selective) and typical, but not pathognomonic, morphological changes in glomerular capillaries in the absence of any identifiable extraglomerular disease process, other than that engendered by the biochemical disturbances which result from proteinuria itself [1]. On the other hand, secondary MCD is defined by the presence of some identifiable extraglomerular disease process occurring concomitantly with the morphologic and functional abnormalities of MCD, irrespective of underlying pathogenetic mechanism. Viewed in this context, secondary MCD takes on several forms.

(i) Secondary MCD wherein the extraglomerular disease process evokes, directly or indirectly, the characteristic changes in permselectivity and morphology. In this circumstance the morphology is similar, if not identical, to primary or 'idiopathic' MCD. Moreover, it is possible, even likely, that similar or identical pathogenetic mechanisms are operative. In this scenario, a distinct etiologic link is presumed to exist between the extraglomerular disease process and the occurrence of MCD. Such a linkage would be strongly supported if cure of the extraglomerular disease lead to the eradication of MCD and if recurrence of the extraglomerular disorder was associated with relapse.
(ii) Primary MCD or its treatment creates an environment which fosters the emergence of the sporadic but spontaneous generation of extraglomerular disease.
(iii) The underlying genetic determinants of susceptibility to MCD also increase susceptibility to a pathogenetically unrelated and distinct extraglomerular disease process.
(iv) The association of MCD and an extraglomerular disease process is purely coincidental.

Of course, the first scenario listed above is most interesting as it affords an opportunity to explore mechanisms common to the primary and secondary forms of disease. The final scenario is difficult to evaluate as the critical appraisal of differences between chance and causal association requires extensive epidemiological information, which is often lacking for uncommon lesions. Thus, reports of an association between MCD and an extraglomerular disease process, which are based on single cases represent anecdotes, even though it would be quite uncommon for two rather rare disease processes to occur together simultaneously.

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The purpose of this presentation will be to catalogue the known secondary forms of MCD in an attempt to characterize them with respect to the nature of the relationship between the extraglomerular disease process and the functional morphologic changes in the glomeruli characteristic of MCD. This subject has also been recently reviewed by Glassock, Adler and Cohen [1].

Characterization of secondary minimal change disease

The six main categories of secondary MCD are listed in Table 1 [1]. While an attempt has been made to be comprehensive, it is possible that individual reports describing an association between the specific extraglomerular disease and MCD may have been overlooked. The majority of the instances in which MCD has been associated with an extraglomerular disease involve neoplastic processes and idiosyncratic, hypersensitivity or toxic reactions to drugs.

Neoplasia

A variety of neoplastic processes have been reported in association with MCD (Table 2) [2–45]. In some, the association is rare enough to suspect that chance alone may have been the operational mechanism underlying the association. In others, the association is clearly contemporaneous and likely causal. Among patients with glomerular disease associated with neoplasia, ~40% have MCD on renal biopsy. As mentioned previously it is possible that some of the described associations between neoplasia and MCD may be the consequence of treatment of MCD (especially cytotoxic drug therapy) predisposing to the emergence of a malignancy.

Hodgkin's disease and non-Hodgkin's lymphoma are among the most frequently reported neoplastic processes associated with MCD [4–19]. Interestingly, reports describing the concurrence of MCD and Hodgkin's disease have decreased in recent years, perhaps due to the more effective diagnostic and therapeutic strategies available for this and related diseases. MCD is a rare complication of Hodgkin's disease occurring in from 1:2000 to 1:10 000 cases. MCD has been associated with both limited (Stage 1) and disseminated (Stage 4) forms of Hodgkin's disease. Therapy of Hodgkin's disease, either by local radiotherapy to regional lymph nodes or by systemic chemotherapy, has often resulted in remission of MCD and recurrences of Hodgkin's disease have been associated with recurrence of MCD [6,7,16,19]. These observations strongly imply a causal relationship between the tumour (or a product of the abnormal neoplastic cells) and the pathophysiological abnormalities involved in MCD. Indeed, it is quite possible that the same clone of cells which are involved in the development of Hodgkin's disease are also involved in the pathogenesis of MCD in both the primary and secondary forms. Such an explanation is more difficult to conjecture for the association of MCD with the other tumours listed in Table 2, except for mycosis fungoides, angiofollicular lymph node hyperplasia, non-Hodgkin's lymphoma and chronic lymphatic leukaemia [9,20,21]. Perhaps, in these instances, the perturbations for MCD have also triggered the oncogenic potential of cells predisposed to neoplastic transformation (e.g. lack of a wild type tumour suppressor gene). Alternatively, lymphocytes infiltrating neoplastic growths could be induced to elaborate factors responsible for abnormal permeability. Whatever the case may be, it is worthwhile to consider potential underlying neoplasia in patients with MCD when atypical features are present such as weight loss, anorexia, lymphadenopathy, haematuria, fever, pleural effusions or skin lesions. Overall, the occurrence of MCD as a complication of neoplastic disorders is quite uncommon. MCD may precede the diagnosis of neoplasia by months or years or may follow the diagnosis of neoplasia by months or years. Some reports have suggested that NK-cell deficiency is associated with the development of MCD in patients with Hodgkin's disease [14].

Table 1. Categorization of secondary MCD (76[a])

- Neoplasia (19)
- Drugs (24)
- Infections (7)
- Atopy (6)
- Superimposed on another renal disease (5)
- Miscellaneous (15)

[a]The number in parentheses indicates the number of specific diseases or clinico-pathologic entities reported to be associated with MCD.

Table 2. Neoplasms associated with MCD (19[a])

- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Leukaemia (chronic lymphatic, intravascular lymphoma)
- Thymoma (with or without myasthenia gravis)
- Renal cell carcinoma
- Mesothelioma
- Bronchogenic carcinoma
- Colon carcinoma
- Pancreatic carcinoma
- Urothelial cancer
- Prostatic carcinoma
- Renal oncocytoma
- Angiofollicular lymph node hyperplasia
- Mycosis fungoides
- Neurilemmoma
- Waldenstrom's macroglobulinemia
- Chordoma
- Lymphoid hamartoma
- Kimura's disease

[a]See references [2–45]; the number in parentheses indicates the number of different diseases associated with MCD.

Drugs

MCD is increasingly recognized as a complication of therapy with a variety of agents [46–63]. These are listed in Table 3. In many cases, a hypersensitivity reaction rather than a direct toxic effect appears to be involved. Nevertheless, it is possible that some of the agents listed in Table 3 may exert their harmful effects on glomerular capillaries through a direct toxic effect (e.g. daunomycin, lithium and interferon). Agents in the non-steroidal anti-inflammatory drug classification can produce heavy proteinuria and nephrotic syndrome associated with glomerular lesions identical to that seen in primary MCD. In most, but not all, cases there is a concomitant acute interstitial nephritis characterized by the influx of polyclonal T and B cells [46–51]. Clinically, the association of NSAID with MCD is also characterized by an abrupt decline in renal function, usually eventuating in acute renal failure. Skin rashes and fever are uncommon.

Recrudescence may occur upon re-exposure to the drug, implying that a cell-mediated hypersensitivity reaction is operative. Withdrawal of the agent is usually associated with full recovery but glucocorticoids may hasten the rate of return of renal function and disappearance of proteinuria. Nevertheless, a clear beneficial effect of steroids on the course of NSAID induced MCD is not yet established. Systemic release of permselectivity promoting factors from activated inflammatory or immune cells may be the basis for the association between drug exposure and MCD. As mentioned above, some compounds may have direct toxic effects on the integrity of the glomerular epithelial cell thus resulting in abnormal glomerular permeability and the effacement of foot processes so characteristic of MCD. It is likely, though not yet proven, that genetic susceptibility to the toxic effects of drugs or to the release of endogenous permeability promoting products plays a role in the association of MCD with drug exposure. Although an accompanying interstitial inflammation is frequently a harbinger of a drug-associated secondary MCD, a few reports have indicated that drugs may result in the lesion of MCD without any accompanying interstitial inflammation [46–51]. Thus, a thorough drug history should be obtained in all patients presenting with nephrotic syndrome due to MCD and, if possible, potentially offending drugs should be discontinued before ascribing the lesion to the 'idiopathic' category.

Table 3. Drugs associated with MCD (24[a])

- Gold
- Antimicrobials (ampicillin, rifampicin, cefixime)
- NSAIDs (ibuprofen, fenoprofen, piroxicam, diclofenac, tolmetin, naproxen, zomepirac, indomethacin)
- Trimethadione
- Paramethadione
- Lithium
- Interferon (α, γ)
- Methimazole
- Tamoxifen
- Enalapril
- Penicillamine
- Probenecid
- Immunizations

[a]See references [46–63]; the number in parentheses indicates the number of specific drugs associated with MCD.

Infections

Although MCD and nephrotic syndrome represents a clinical state of enhanced susceptibility to infection, the causal relationship between an infectious disease and the development of MCD has been suspected only rarely [64–74]. The infectious diseases in which MCD is thought to have occurred on a secondary basis (rather than vice versa) are shown in Table 4. The precise relationship between the infectious disease and MCD in these circumstances is unknown. It is possible that these infectious agents activate a subset of lymphocytes capable of elaborating permeability factors. Often, with appropriate anti-microbial therapy of the underlying infectious disease, the MCD will abate.

Atopy

A heightened allergic reactivity to environmental agents has long been associated with MCD [75–81]. Indeed, many authors have described the onset of MCD or its relapse as being clearly related to an allergic reaction (such as bee sting or other envenomations).

It is possible that the phenomenon of IgE-ediated hypersensitivity is pathogenetically related to the development of MCD, although IgE deposition is not noted in the renal lesions. IgE levels are elevated in ~50% of patients with MCD. Table 5 lists the more common associations of atopy with MCD (including

Table 4. Infections associated with MCD (7[a])

- Syphilis
- Tuberculosis (?)
- Human Immunodeficiency Virus
- Mycoplasma
- Ehrlichiosis
- Echinococcus (hydatid disease)
- Schistosomiasis

[a]See references [68–74]; the number in parentheses indicates the number of specific infections associated with MCD.

Table 5. Atopic agents associated with MCD (6[a])

- Pollen
- Dairy products (milk)
- House dust
- Pork
- Bee stings
- Poison oak/ivy

[a]See references [75–81]; the number in parentheses indicates the number of atopic diseases or circumstances associated with MCD.

eczema, hives, contact dermatitis, hay fever and rhinitis). The avoidance of potential allergens, such as dairy products, pork, house dust and pollen can occasionally be associated with prolonged remissions of MCD. Some reports have described that seasonal recurrences of MCD can be linked to an allergic disorder [80]. Unfortunately, treatment of individuals displaying a background of atopy accompanying MCD with cromoglycate has been quite unsuccessful. Some reports have described an underlying genetic susceptibility to both the allergic disorder and MCD (e.g. HLA-B12), and thus it is possible that the association of atopy and MCD is more fortuitous than direct.

Associated with other glomerular or renal diseases

MCD and nephrotic syndrome may be observed in association with other renal disease [82–88]. These are listed in Table 6. These associations probably occur in excess of that expected by chance alone and may be due to some common genetically based susceptibility. Extensive mesangial IgA deposition may be seen in some instances of MCD [86]. These patients behave more like MCD than IgA nephropathy in that they are responsive to glucocorticoids and have a benign prognosis. New onset type 1 insulin-dependent diabetes mellitus is associated with the development of nephrotic syndrome due to MCD in rare circumstances [85]. This lesion appears to be responsive to glucocorticoids. Whether the diabetic state, *per se*, induces abnormalities, which result in the lesion of MCD or whether the concurrence of these two lesions is the result of some common genetic susceptibility remains uncertain [84]. Based on current observations, the latter possibility appears more likely. With an incidence of 1:300 for type 1 diabetes and 1:50 000 for MCD, the two disorders would be expected to occur together by chance alone in 1:15 000 000 individuals. Very rarely MCD may be a part of the presentation of systemic lupus erythematosus or occur as a complication of autosomal dominant or recessive polycystic kidney disease. In both circumstances, the lesion appears to be responsive to glucocorticoids and may merely be the superimposition of 'primary' MCD on the systemic disease [82,83].

Miscellaneous

A large number of reports (usually single case reports) have appeared describing the association of MCD with another disease process [89–105]. These vary widely from acute decompression illness to vigorous exercise. The exact relationship between the concurrence of the extraglomerular disease and MCD remains unknown, and many of these instances may present chance rather than causal associations. A list of the miscellaneous disorders associated with MCD is presented in Table 7.

Table 6. MCD superimposed on another renal disease (5[a])

- IgA nephropathy
- Systemic lupus erythematosus
- Diabetes mellitus (new onset type 1)
- Autosomal dominant and recessive polycystic kidney disease
- HIV associated nephropathy

[a]See references [82–88]; the number in parentheses indicates the number of specific diseases associated with MCD.

Discussion

The extraglomerular disease processes, which have been associated with MCD are both numerous and diverse. It is difficult to discern a common theme in the spectrum of disease associations. Nevertheless, the associations between MCD and neoplasia and drugs strongly suggest that some perturbation of cellular immunity is involved. It is possible that the extraglomerular disease stimulates a subset of lymphocytes to elaborate permeability factors identical to that responsible for the primary lesion. Alternatively, deficiency states, such as natural killer cell deficiency, may give rise to perturbations in the immune system favouring the elaboration of permeability factors. Direct demonstration of some commonality in pathogenesis between primary and secondary forms of MCD must await the identification and characterization of putative permeability factors and the definition of the cellular origin of these permeability promoting substances. From a clinical perspective, it is important to keep in mind that, in some instances, apparently 'idiopathic' MCD may in fact represent a lesion arising secondary to an extraglomerular disease process. In many instances, the association between the extraglomerular disease process and MCD is quite obvious; on the other hand, the clinical manifestations of the underlying extraglomerular disease process can be quite subtle. Thus, patients should be thoroughly evaluated for potential underlying diseases, particularly neoplasia and drug exposure, when atypical features are present (such as weight loss, anorexia, lymphadenopathy or acute renal failure). When interstitial inflammation is found in association with nephrotic syndrome and MCD, drug exposure,

Table 7. Miscellaneous diseases associated with MCD (15[a])

- Sclerosing cholangitis
- Sclerosing mesenteric inflammation
- Vigorous exercise
- Acute decompression sickness
- Sarcoidosis
- Grave's disease
- Thyroiditis
- Vasculitis
- Partial lipodystrophy
- Myasthenia gravis (without apparent thymoma)
- Renal artery stenosis
- Bis-albuminaemia
- Guillain–Barre syndrome
- Dermatitis herpetiformis
- Melorheostosis, mesenteric fibrosis, haemangiomas

[a]See references [89–105]; the number in parentheses indicates the number of specific miscellaneous diseases associated with MCD.

particularly to non-steroidal anti-inflammatory agents, should be strongly suspected. Discontinuance of the drug or successful treatment of the underlying disease process (such as chemotherapy for neoplasia or anti-microbial therapy of infections) often results in a remission of MCD and a nephrotic syndrome.

The prognosis for secondary MCD is generally favourable, although extensively influenced by the nature of the extraglomerular disease process. For example, Hodgkin's disease associated with MCD that is refractory to chemotherapy would carry a very adverse prognosis. MCD associated with other renal diseases (such as IgA nephropathy, insulin-dependent diabetes mellitus, systemic lupus erythematosus or polycystic kidney disease) generally has a favourable prognosis similar to that observed with a primary MCD.

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