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Paraneoplasia as an Epigenetic Reflection of Systemic Dimensions Of Potential Neoplastic Spread

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Abstract: Paraneoplasia as an essential system of involvement inherent to genetic attributes of neoplastic cellular proliferative events might actually involve an epigenetic process in a context of, however, systemic progression by the neoplasm. Indeed, a strict referential series of events as steps in systemic involvement of the patient by a proliferating and infiltrative neoplasm might simply constitute modes of how such a neoplasm is, itself, a primarily systemic phenomenon with paradoxically focal manifestations that implicate however, progressive regional spread. In this sense, neoplasia might primarily constitute a process of systemic dimensions that is manifested also as a systemic phenomenon of paraneoplasia. In addition, one might speak of paraneoplastic syndromes as, for example, myasthenia gravis or endocrine manifestations, that parallel an associated neoplasm as a focal lesion of systemic dimensions. Indeed, genetic and epigenetic manifestations of neoplasia would involve different aspects of a phenomenon of systemic evolution that is not only manifested focally or regionally but is progressive mainly in terms of a focality that evolves in a strictly systemic context of genesis and epigenesis.

Key words: Potential ,neoplastic,spread,paraneoplasia,epigenetic reflection,systemic, evolution

INTRODUCTION

Paraneoplastic syndromes reflect staged antigenic exposure concomitant with generation of the neoplastic cells: The mechanisms concerned with unmasking of antigenic sites in inducing reactivity in a paraneoplastic syndrome, affecting the central and peripheral nervous system, would show features of specific localization in some cases (as with Purkinje cell degeneration in the cerebellum), or else an encephalomyeloneuritis might develop[1].

Such distribution of neurologic lesions would be associated with a specific antigen that is unmasked on the tumor cell surface, in such a way as to elicit a powerful and specific immune response to that neurally associated antigen [2]. This might even result in demyelination in the brain as a paraneoplastic disorder[3].

What mechanisms might account for such an effective stimulation of the immune system, although only on relatively uncommon occasions?

It may be true that neoplastic cells are occasionally associated with some altered presentation of the particular antigen in question, particularly, for example, with reference to foci of tumor cells undergoing progressive cell damage or necrosis, as in small cell carcinoma of the lung.

Thymoma significantly involves the thymus as a centrally operative organ that fashions the immune system itself. In the case of myasthenia gravis, the antibody response is often made up of several antibody specificities directed against multiple different antigenic sites on the extracellular aspect of the acetylcholine receptor. In addition, it is interesting that, in paraneoplastic forms of myasthenia gravis, antibodies to striated muscle antigens are often found located mainly in the sarcoplasm or sarcoplasmic reticulum. Indeed, these antimuscle antibodies, once generated, usually play a significant pathogenic role since normally the target antigens in normal striated myofibers are beyond reach of them. Inflammatory myopathies as a highly heterogeneous group of conditions would also constitute a paraneoplastic form of susceptibility in certain patients[4,5], including also patients with inclusion body myositis[6].

Lesions such as small cell lung carcinoma and presumably several other types of neoplasm associated with paraneoplasia, would involve stimulation of an autoimmune response to normal tissues as forms of degeneration of the tumor cells that pass through various stages of more complete exposure of antigenic sites. For example, small cell carcinoma might constitute a potential initiator of ganglionic nicotinic acetylcholine receptor autoimmunity in inducing several types of paraneoplastic syndromes involving cholinergic systems and even autonomic neuropathy, seizures, dementia and movement disorders[7]. Also, resolution of the paraneoplastic syndrome might occur on excision of the primary neoplasm as in the case of limbic encephalitis associated with small cell lung cancer[8].

As a fundamental principle, therefore, neoplasia would implicate the staged antigenic exposure to the immune system, at multiple different epitope sites. Perhaps, such a phenomenon might implicate an immune system that is inherently directed against normal antigenic sites in so constituting a paraneoplastic syndrome. The often-involved nervous system in such paraneoplastic syndromes would relate mainly to the common incidence of specific primary tumor types such as small cell lung carcinoma.

Analogy of the immune/inflammatory response against neuronal subpopulations in both viral infections and paraneoplastic syndromes : The inflammatory component of paraneoplastic syndromes, involving, for example, the cerebellar cortex or the peripheral nervous system or as a combined encephalomyelitis/neuropathy, would develop in some cases of small cell lung carcinoma, or even malignant melanoma, as a predominantly neuronal type of injury.

Such paraneoplastic lesions would implicate an immune response incorporating a specific neuronally induced injury mediated by an inflammatory component. In fact, the inflammatory limb of the response would however appear to involve an antibody response as a primary or initial sequence of events.

A cross reaction between antigens present both on the primary neoplastic cells and neurons would result in an exquisitely directed attack on highly selective subpopulations of neurons in the central or peripheral nervous system or both.

The antibody combining to epitopes on normal neurons would be especially liable to elicit an inflammatory response as a main mechanism of neuronal injury in subsequently inducing neuronal degeneration, including especially vacuolization and chromatolysis, neuronal death in addition to gliosis and microgliosis as diffuse infiltrates or nodules.

It is this strict sequence of paralleling events, as seen classically in cases of neuronal infection, that would be especially relevant in terms of the highly selective inflammatory response directed against individual neurons or specific subpopulations of neurons. Such an immune/inflammatory response would render possible a distinction between neurons in the central or peripheral nervous system, as with subpopulations of neurons in the brain stem or cerebellar cortex or Purkinje cells. For example, autoantibodies might develop against mGluR1 in patients with Hodgkin's disease that would result in cerebellar coordination deficits affecting acute and plastic responses of Purkinje cells involving chronic neurodegeneration[9,10]. Also, a strong association between anti-Tr antibodies and paraneoplastic cerebellar degeneration in patients with Hodgkin's disease might develop in a context of antineuronal autoimmunity[11,12].

The immune response appears to involve antibody binding to a specific antigenic epitope on selected neurons that is strictly related to the cell membrane. Subsequent to internalization, such a binding process might a promote a selectively directed inflammatory response that is generated and sustained in specifically inducing loss of given neuronal subpopulations. In fact, a basic series of mechanisms having much in common with those underlying the host response to viral infections in the nervous system would perhaps be operative in neurologic paraneoplastic syndromes.

Does a common basic pathogenesis in neuronal cell injury and death underlie neurodegenerative disorders and viral infections of the nervous system?: It is conceivable that the specific pathogenic mechanisms inducing cell damage in cases of viral infection, as seen particularly in the central nervous system, would be fundamentally analogous to pathogenic mechanisms of cell damage as seen in the classically recognized examples of neurodegeneration.

Certainly, phenomena such as neuronal cell lysis, death and replacement gliosis would be constitutionally identical in nature in both viral infections of the CNS and in neurodegeneration.

It might additionally appear significant that neuronophagia is central to both pathways of neuronal damage and of neuronal cell death. Such phenomena would be primarily directed against a specific target or targets in the neuron itself. A main difference would be the associated, florid inflammatory reaction, as initially centered on blood vessels in viral encephalitis, but absent in cases of neurodegeneration. Microglial response would constitute an integral part not only of viral encephalitis, but also of classic neurodegeneration, as with the neuritic plaques of Alzheimer's disease, or with loss of anterior horn neurons in amyotrophic lateral sclerosis.

Neurodegeneration would constitute, in general outline, but particularly in terms of several specific pathogenic steps in executive cell injury, a form of neuronal involvement essentially identical to that occurring in viral infections of the nervous system

Such a common mechanistic basis for neuronal cell damage, death, removal and replacement by gliosis might evolve not only in terms of the actual process of neuronal dissolution, but especially in reference to definite stages in the pathogenesis of induction of such cell injury and death.

It is perhaps such aspects of neurodegeneration, particularly in terms of lack of an associated inflammatory component, that would primarily distinguish pathologically and pathogenically viral infections of the nervous system from other various systems of progression of neuronal cell injury and loss.

Can viral infection underlie some cases of paraneoplastic syndromes involving the nervous system?: It would appear possible that some basic and distinctive phenomenon underlies the antibody response against both the antigens (such as Yo and Hu) on primary neoplastic cells and the neurons affected in the associated paraneoplastic syndromes of the nervous system. Also, for example, aberrantly expressed recoverin, as a retina specific Ca2+ binding protein, would be involved in the G-protein coupled receptor kinase-dependent cellular regulation in these cancer cells [13].

Also, anti-recoverin antibodies would induce apoptosis through the mitochondrial pathway involving caspases 9 and 3[14].

The often observed failure to induce a neurologic paraneoplastic syndrome by passively injecting these antibodies, or by actively stimulating antibody production, would be consistent with some essential underlying series of mechanisms directing antibody response to both the primary neoplasm and to neurons in the central and/or peripheral nervous system. In view of the associated inflammatory response as seen especially in cases of encephalomyelitis and in paraneoplastic cerebellar degeneration, it would appear likely that an agent, possibly an infectious agent, might underlie pathology affecting both lesions.

Also, the highly distinctive nervous system involvement, particularly as a highly selective involvement of specific neuronal subpopulations, would perhaps associate with a possible primary neoplasm rather than, conversely, be a function of primary neuronal pathology.

In addition, many cases of paraneoplastic syndromes develop several years before detection of the primary neoplasm and also such a neoplasm often constitutes an early small focus.

Small cell lung carcinoma, a lesion notorious for its strong tendency for early systemic spread would constitute one possible case in point. Various mechanisms implicating actual genesis of the primary neoplasm might operate concurrently with, or even primarily, to induce damage injury to highly specific neuronal subpopulations.

One possible mechanism for example, would involve a viral infection that induces both development of the primary neoplasm and neurologic paraneoplastic syndromes evolving concurrently or in a temporally sequential fashion even possibly based on an epigenetic phenomenon of association.

Simple cross-reactivity of antibody production and action may not be primarily causative in inducing associated carcinogenesis. In such paraneoplastic patients, an immune/inflammatory response to specific single or multiple neuronal subpopulations in the nervous system would operate towards the slower evolution and progression of the neoplasm. Such a neoplasm would develop in an overall dimension of a paraneoplastic syndrome involving especially the central nervous neurodegeneration.

Certainly, the neurologic paraneoplastic syndromes would be essentially centered on the neuron as the essential subunit target for such an immune/inflammatory response. Such a pattern of pathologic involvement would even perhaps implicate a highly specific neurotropic phenomenon as classically occurring with viral infections of the nervous system.

Paraneoplasia towards mediation of nature and effects of neoplastic cell proliferation and infiltration: Upregulation of COX2 (cyclooxygenase 2) expression via an upregulation of mRNA production would be particularly significant in carcinogenesis since COX2 constitutes an inducible form of the cyclooxygenase[15].

The mode of association of inducible paraneoplastic phenomena would constitute an autonomous and essentially non-responsive series of processes implicating a whole array of mechanisms inherently responsive to the process of genesis and progression of a neoplasm, as seen for example with primary pancreatic carcinoma[16].

Given the full context of certain epigenetic mechanisms closely associated with the neoplasm, in terms of strict cell proliferation and infiltration, might help characterize specific types of paraneoplasia as mechanistic support to evolution of the neoplastic process itself.

In terms hence of a paraneoplasia that not only supports but also actively mediates phenomena that effectively influence direct neoplastic cell proliferation and infiltration, angiogenesis might constitute a regional response to neoplastic cells inducing also enzymatic reactions and specific metabolic pathways of predilection.

Hence, it might be relevant to consider development and progression of a neoplasm as one intrinsically implicating a full array of active paraneoplastic processes that not only support neoplastic cell proliferation and infiltration but materially characterize these processes dynamically, biochemically and as potential response to therapeutic intervention.

Autoimmunity and paraneoplasia as distinct manifestations arising from tumor cell proliferation and based on spectral changes of t-lymphocyte receptors: Induced apoptosis of T lymphocytes, when these interact with a tumor cell microenvironment, might, in a final analysis, constitute a phenomenon beyond programmed cell death of T-lymphocyte receptors[17], both in terms of target and constituent participants of a progressive cell death involving a positive feedback pathway that induces autoimmunity or paraneoplastic manifestations. For example, CD8-positive cytotoxic T cells would appear involved in the development of paraneoplastic neurological syndromes with anti-Hu antibodies, as seen in many patients with limbic encephalitis associated with small cell lung carcinoma[18].

Indeed, modification steps directing such a transformation of the immune response to tumor cell proliferation would perhaps implicate a process of modulated immune response in a step-by-step degradation of tumor cell biology evolving as a system involvement in a microenvironment that promotes carcinogenesis. In this regard, for example, autoimmune paraneoplastic syndromes are commonly encountered in patients with myelodysplastic syndromes[18] or even with multiple myeloma[20,21].

Ttumor-cell-directed immunity might constitute a full constellation of mechanisms promoting constitutional T-lymphocyte receptors and also expansion of cytotoxic T lymphocyte populations[22]. Besides considerations of phenomena of T-lymphocyte-induced lysis and cytotoxicity and of suppressor T-lymphocyte action, much of the dynamic pathobiology of the T lymphocyte might largely evolve as a direct function of such T-lymphocyte receptors.

In terms, indeed, of actual mechanistic degradation of the T-lymphocytes themselves, it is the caspase-induced pathways involving particularly the ubiquination of such receptors that would constitute elements of progression along pathways of apoptosis or conversely of failure of such immune response. This would perhaps implicate aberrant autoimmunity or paraneoplasia closely related to tumor biologic evolution.

Antigenic exposure on tumor cells in immune stimulation to account for the paraneoplastic syndrome of myasthenia gravis associated with thymoma: A particularly interesting aspect of paraneoplasia is the possible development of an immune response to the neoplasm, in the added integral context of native antigen reactivity.

Paraneoplastic syndromes would directly implicate significant immune reactivity against components of the tumor even though such antigenicity would appear to arise as a natural consequence of native tissue antigenicity. In this regard, the cellular antigens constituting a thymoma would perhaps associate with myasthenia gravis in implicating staged antigenic epitope exposure as presented by acetylcholine receptors at the neuromuscular junction. In addition, anti-cytokine autoantibodies would tend to develop against Interferon alpha, Inteferon omega and Interleukin-12 in patients with thymoma and/or myasthenia gravis; such antibody titers would increase sharply if the tumors recurs[23].

The antibody response in myasthenia gravis with thymoma would tend to be heterogeneous[24], with various antibody types directed against various extracellular sites on the acetylcholine receptor. Such a phenomenon of multi-antigen specificity in antibody-directed responsiveness would be suggestive of effective exposure to an immune system, as related to Acetylcholine antigenic sites in cases of small cell carcinoma. This is true in spite of the partial antigenic epitopes present on such tumor cells. Indeed, paraneoplastic syndromes might represent particularly effective forms of exposure of antigens, as in fact typically documented with thymomas.

It is perhaps such effective stimulation of the immune system accounting for secondary consequences of reactivity of a heterogeneous antibody response against multiple antigenic sites on normal acetylcholine receptors that would result in clinical manifestations of myasthenia gravis. Also, the P/Q type voltage-gated calcium channels of the cerebellar molecular layer would constitute an immunological target in paraneoplastic cerebellar degeneration development evolving in patients with the Lambert-Eaton myasthenic syndrome[25,26].

Highly analogous features of the immune/inflammatory response against neuronal subpopulations in both viral infections and paraneoplastic syndromes: The inflammatory component of nervous system lesions, (whether in the central nervous system, as affecting cerebellar cortex, or in the peripheral or autonomic[27] nervous system or even as a combined encephalomyelitis/neuropathy) in cases of paraneoplasia associated with small cell lung carcinoma, could perhaps operatively affect patients suffering from other neoplasms, including melanoma[28].

In a sense, paraneoplastic lesions would implicate integrated combinations of specifically directed immune responsiveness incorporating neuronal injury with a participating inflammatory component. In this regard, for example, a cutaneous lymphocytic vasculitis might be a presenting feature in patients suffering from acute lymphoblastic leukemia [29]. Also, urticarial vasculitis has been specifically reported as aparaneoplastic manifestation[30].

In fact, the inflammatory paraneoplastic component-response might constitute systems of neuronal injury involving a definite antibody response, primarily initiating both neoplastic and paraneoplastic involvement. In this sense, for example, Nuclear Factor KappaBeta activity might prove to be a late event in carcinogenesis related to tumor development in patients with renal cell carcinoma[31]. Also, for example, an acute demyelinating polyneuropathy might develop in association with renal cell carcinoma that dramatically improves on giving intravenous immunoglobulins[32].

Indeed, a cross reactivity involving antigens, both on the primary neoplastic cells and on neurons, would result in an exquisitely directed attack on highly selected neuronal subpopulations.

The antibody combining to epitopes on normal neurons apparently would be prone to elicit an inflammatory response in a context of induced neuronal injury leading to degeneration, as evidenced by vacuolization and chromatolysis. Subsequent neuronal death and loss, with replacement gliosis and accompanying microgliosis, would include diffuse infiltrates as well as actual microglial nodule formation.

It is in such a context of a strict sequence of events paralleling neuronal infection, as with viral types, that the inflammatory response would be directed against individual neurons as members of specific subpopulations of neurons. The immune/inflammatory response would often distinguish between neurons in the central or peripheral nervous system, as seen with brain stem neurons or the Purkinje cells of the cerebellar cortex in a context of paraneoplasia.

The immune response would involve an antibody binding to specific antigenic epitopes on selected neuronal subgroups as individual cells including specific sites on the cell membrane. Such complex transformation might evolve in the specific context of an inflammatory response generated and sustained within integral neuronal subpopulations that are injured and eventually lost. A basic series of mechanisms having much in common with those underlying the host response to viral infections in the nervous system might indeed help account for such operative progression in evolution of paraneoplastic syndromes.

CONCLUSIONS

One might consider epigenesis of a neoplasm as primarily systemic, but with focal manifestations towards progression of such a neoplasm. Indeed, one would perhaps view neoplasia as the systemic genesis of a focal lesion with, in addition, subsequent progression in systemic terms. A systemic dimension for the neoplasm would appear to incorporate also a focality and a regionality of involvement paradoxically characterizing the subsequent progressive systemic dimensions of involvement of the patient by that neoplasm. One might consider genesis and epigenesis of events of neoplastic progression as integral components of a single set of forms of involvement whereby the neoplasm is partly defined also as epigenetic or paraneoplastic events

Even in terms of evolving progression, one might perhaps consider infiltrative spread and metastasis by a neoplasm as simply an expression that epigenetically gives a systemic dimension to such neoplastic focality and regionality in progression.

In fact, paraneoplasia and neoplastic infiltration and spread, might constitute one integral phenomenon of epigenesis strictly reflecting the nature of progressive genesis of a lesion primarily arising focally or regionally.

Indeed, one would perhaps consider neoplasia as simply being manifested clinically as an epigenesis in systemic progression via infiltrative and metastatic spread or alternatively as an epigenesis of paraneoplastic type.

Even in terms of such a neoplastic focality or regionality that would evolve largely within a systemic context, epigenetic events would strictly help characterize a neoplastic lesion beyond simple concepts of spread multifocally or systemically. Neoplasia would perhaps constitute multiple different ways of variable systemic involvement arising from integrally evolving epigenetic effect characterizing further progression of a neoplasm that arises focally or regionally.

Antigenicity, as a purely or largely inflammatory reactivity related to specific antigenic epitope sites on individual neurons, would perhaps operate as strict neuronal subpopulations affected by an evoked inflammatory response. Paraneoplasia would progress not only epigenetically but also implicate a correlative substitution with neogenesis and especially as a characterized form of cell injury.

Indeed, one might consider paraneoplasia not only as a byproduct of exposed antigenic epitopes but also as a phenomenon arising consequent to cellular injury developing subsequent to evolving neogenesis or carcinogenesis. An integral process of evolving progression might implicate not simply transforming injury relative to an immune responsiveness affecting specific neuronal subpopulations but especially a series of mechanistic pathways accounting for the development of the neoplasm paralleling the paraneoplastic process itself.

It is perhaps significant that paraneoplasia would constitute a potential basis for progression of the neoplastic process strictly as a phenomenon of evolving epigenesis somehow intrinsic to systemic neoplastic spread in the body. It is perhaps in terms of such systems of supporting influence involving neoplastic cell proliferation and infiltration and also mechanistic

pathways of dynamic progression of the neoplasm that one would define paraneoplasia as a fundamental attribute of neoplastic genesis and of its subsequent development.

Indeed, if one were to consider paraneoplasia as a strict epigenesis that is responsible in its own right to subsequent characterization, paradoxically, of the biologic progression and spread of the neoplasm in question, it might prove itself to be a significant aspect of neoplasia. In this sense, perhaps, the actual attributes pathobiologically of neoplastic cells as proliferative and infiltrative systems of spread might simply arise and develop as mechanisms of epigenesis tied up somehow with a process of carcinogenesis as essential malignant transformation. Indeed, one might perhaps view neoplasia as a phenomenon of spread epigenetically related to pathways of transforming evolution implicating systems of proliferation and of infiltration somehow characterized biologically by such paraneoplasia. Perhaps understanding features of paraneoplasia as syndromes inherently arising from affects of neoplastic spread might actually help redefine such neoplastic spread as a phenomenon of epigenetic conditioning of neoplastic tissue in terms of systemic involvement and evolution. Indeed, paraneoplasia might, paradoxically, condition the defining pathobiologic basis for neoplastic cell proliferation and spread in terms of both trophic and mechanistic systems of evolving progression. In simple terms, understanding epigenesis as a paraneoplasia would perhaps help redefine neoplastic progression as systemic conditioning strictly characterizing such neoplastic progression.

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