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Monoclonal Gammopathy of Undetermined Significance

Monoclonal gammopathy of undetermined significance (MGUS) is defined as the presence of a monoclonal immunoglobulin (M-spike or M-protein) with a serum concentration < 3 g/dL, little or no monoclonal light chain protein in the urine, absence of lytic bone lesions, anemia, hypercalcemia or renal insufficiency related to the monoclonal protein, and ≤ 10% plasma cells in the bone marrow. MGUS (formerly referred to as "benign monoclonal gammopathy") is relatively common, with a prevalence of 2% in patients older than 49 years and 3% in patients over 70. Previous studies had indicated a slight risk of progression to multiple myeloma or B-cell lymphoma. A recent study from the Mayo Clinic followed 1384 patients with MGUS over a 34 year interval to further characterize the biology of this disorder.[1] The patients were seen at the Clinic from 1960 – 1994. All were evaluated by serum protein electrophoresis, followed by serum immunofixation or immunoelectrophoresis. Bone marrow evaluation was performed only in those with an M-spike greater than 2.0 g/dL or those with unexplained anemia, hypercalcemia, renal insufficiency or bone pain. Approximately 30% had urine protein electrophoresis and/or immunofixation. Patients were advised to have serum protein electrophoresis annually. Inpatient and outpatient medical records, as well as all death certificates, were reviewed. The median follow-up period was 15.4 years (range 0 – 35 years).

All patients fulfilled the criteria for MGUS defined above. The size of the M-protein ranged from unmeasurable (visible band on gel, but below resolution of densitometer tracing) to 3.0 g/dL. The M-protein immunoglobulin class was IgG in 70%, IgA in 12%, IgM in 15%, and biclonal in 3%. In patients who had quantitative immunoglobulin assessment, the uninvolved (polyclonal or background) immunoglobulin concentration was suppressed in 38%. Bone marrow examination was performed in 160 patients (12%). The prevalence of plasma cells ranged from 0 – 10% (median 3%). During the study period, 963 (70%) died. Progression to multiple myeloma, plasmacytoma, lymphoma with IgM gammopathy, macroglobulinemia, chronic lymphocytic leukemia (CLL), or amyloidosis occurred in 115 patients (8%). The cumulative probability of progression was roughly1% per year (10% at 10 years, 21% at 20 years, and 26% at 25 years). Compared to age-matched controls, the relative risk for myeloma was 25.0, IgM-associated lymphoma 7.8, macroglobulinemia 46.0, and primary amyloidosis 8.4. The relative risk for CLL was not increased. The M-protein disappeared in 66 patients (5%), all of whom had low initial values. In 39 of these cases, the disappearance of the M-protein coincided with therapy for progression to myeloma/lymphoma or treatment of a non-neoplastic condition (e.g. vasculitis or immune thrombocytopenia). In the remaining 27 patients, the M-protein resolved spontaneously. In 19 patients, subsequent evaluation indicated that initial immunofixation or immunoelectrophoresis studies suggesting an M-protein were incorrectly interpreted ("lab error").

As indicated in the table below, the risk of progression to myeloma or related malignancy was directly related to M-protein concentration at the time of initial diagnosis. In addition, patients with an IgA or IgM M-protein were more likely to progress than those with monoclonal IgG. The prevalence of bone marrow plasma cells, reduction in one or more uninvolved immunoglobulins (by quantitative immunoglobulin measurement), or the presence of monoclonal urinary light chain were not risk factors for progression.

The authors concluded that patients with MGUS are more likely to die of an unrelated disease than as a result of progression to myeloma or other related disorder. While the study failed to provide evidence that monitoring improves survival, the authors recommend annual serum protein electrophoresis in patients with MGUS to minimize the risk of renal failure or pathologic fractures developing in unrecognized multiple myeloma.

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MGUS
Risk of Progression to Myeloma or Related Disease

Initial M-Protein Value (g/dL)	10 Year Risk (%)	20 Year Risk (%)
≤ 0.5	6	14
0.6 –1.0	7	Not stated
1.1 – 1.5	11	25
1.6 – 2.0	20	41
2.1 – 2.5	24	49
2.6 – 3.1	34	64

John D. Benson, MD

1. Kyle RA *et al*. A Long-Term Study of Prognosis in Monoclonal Gammopathy of Undetermined Significance. *N Engl J Med* 2002; 346:564-9.

Tubal (Ciliated Cell) Metaplasia

We've gotten a few calls lately about "tubal metaplasia" diagnoses on Pap smears.* Metaplasia refers to the non-neoplastic replacement of one type of mature ("adult") tissue by a different type of mature ("adult") tissue, that is inappropriate for that site. Metaplasia often occurs in the setting of tissue response to injury or irritation (e.g. "incomplete intestinal metaplasia" in the setting of chronic gastritis or reflux esophagitis). The internal female genital tract is frequently subject to epithelial metaplasia, in which the epithelial cells lining a surface or gland lumen are abnormal (cf. *atypical*) in that they resemble cells which normally occur on surfaces or in glands from a different part of the genital tract. (This is not surprising given the shared embryologic ancestry of the müllerian duct derivatives (fallopian tubes, ovaries, uterus, and upper vagina) and the ovarian surface epithelium (mesothelium) with associated subjacent cortical stroma.) [1]

Ciliated cells are ubiquitous to the female genital tract. While most commonly associated with the fallopian tube, they also line the outer surface of the ovary and can be found in the endometrium and endocervix. In the endometrium and endocervix, ciliated cells represent a distinct minority of the glandular cell population, and are scattered amidst more common proliferative endometrial or mucinous endocervical columnar cells. However, on occasion, ciliated cells may predominate – creating an abnormal histologic appearance termed "tubal (or ciliated cell) metaplasia". This phenomenon has been long recognized by surgical pathologists evaluating endometrial biopsies. It is particularly common in women receiving hormone replacement therapy. Ciliated cell metaplasia may superficially resemble well differentiated endometrial adenocarcinoma, particularly when it is superimposed on an endometrium with mild glandular architectural variability (e.g. "disordered proliferative endometrium" which is also commonly seen in women undergoing hormone replacement therapy). Histologic criteria have been developed to assist in distinguishing these two entities, but occasional cases can be problematic. [1]

With improved techniques for cytologic evaluation of the endocervical canal, pathologists have rediscovered the presence of "tubal metaplasia" in the endocervix. The presence of cellular clusters of "abnormal" (meaning different than the usual mucinous endocervical epithelium, rather than atypical) columnar cells on smears prepared with the newer instruments led to increased interpretations of "glandular atypia" or "atypical glandular cells of uncertain significance (AGCUS)". Follow-up biopsies revealed that areas of "tubal metaplasia" were the source of the abnormal cells. In one study of 50 cases of "endocervical glandular dysplasia", tubal metaplasia was found in 66% of cases followed by cervical cone biopsy or hysterectomy, and in 90% of cases followed by cervical biopsy or endocervical curettage. [2] No clear-cut predisposing factors for endocervical tubal metaplasia have been identified. Indeed one study found tubal metaplasia in an entire series of 25 hysterectomy specimens from women without a history of cervical disease, subjected to complete sampling of the endocervical canal. [3] The upper portion of the endocervical canal was the most common site of ciliated cells. Although cytologic

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criteria for distinguishing tubal metaplasia from glandular dysplasia and adenocarcinoma have been suggested, the practical application of these can present a challenge to the (cyto)pathologist. [2,3] In some cases, it may be prudent to recommend follow-up smears or endocervical curettage. [3]

So what should YOU do when you encounter a pathology report with a diagnosis of "tubal metaplasia"? First of all, it is important to be aware of what tubal metaplasia **is**, and what it **isn't**. Tubal metaplasia **is** a benign condition, perhaps reactive – or perhaps an exaggeration of normal histology. It **is** also a source of "false positive" Pap smears, which if not recognized may result in an interpretation of "atypical glandular/squamous cells of uncertain significance" or even "dysplasia". It **is not** a neoplastic, dysplastic, or pre-neoplastic condition. Second, know your pathologist (and his/her limitations). The pathologist who diagnoses "tubal (ciliated cell) metaplasia" without any comment or disclaimer is indicating that he/she recognizes abnormal (but benign) epithelial cells which fit his/her criteria for the entity under discussion – and that no further work-up or evaluation is required. If you are comfortable with the pathologist performing the interpretation, and the patient has no findings suggesting a malignant process, no further evaluation is required. (If you are NOT comfortable with the pathologist interpreting the specimen, I would suggest you ask for another opinion – either intramural or referral to another department.) If the report has a comment or statement indicating concern about possible "dysplasia" or "atypical hyperplasia", I suspect there would also be an explicit recommendation for further evaluation or follow-up. I would suggest giving careful consideration to that recommendation. Finally, know your patient. If the clinical presentation suggests a malignant disease, but the pathology report is "benign", contact the pathologist and share what you know in the context of what (s)he sees. Reviewing slides armed with pertinent clinical information can yield dividends for all concerned. In addition, the possibility of "sampling error" always exists. A diagnosis of "focal tubal metaplasia in **scant** fragments of benign endocervical mucosa" might not be reassuring enough in a patient with an ulcerating cervical mass. Re-biopsy should be strongly considered. *(These comments obviously apply to all sorts of diagnostic studies, but I thought they were worth repeating here.)*

John D. Benson, MD

* In reviewing this article prior to publication, Dr. Keith Nance correctly pointed out that under the Bethesda 2001 classification system, "tubal metaplasia" would actually appear as a supplemental comment, associated with an interpretation of "Negative for dysplasia". Some pathologists may simply observe the tubal metaplasia and not comment upon it at all (thus relieving you of worry, but depriving you the opportunity to appreciate the challenges and subtleties of Pap smear interpretation).

References

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3. Babkowski RC *et al*. The Effects of Endocervical Canal Topography, Tubal Metaplasia, and High Canal Sampling on the Cytologic Presentation of Nonneoplastic Endocervical Cells. *Am J Clin Pathol* 1996; 105:403-10.

WHO's Next

The classification of non-Hodgkin's lymphoma has been a continuing source of confusion, frustration, and even amusement to pathologists and clinicians alike. [1, 2] Physicians of my generation were first introduced to the Rappaport system which recognized 4 basic "cell types" (well differentiated lymphocytic, poorly differentiated lymphocytic, stem cell (e.g. Burkitt's), and histiocytic) which could occur in 2 patterns – nodular or diffuse. Lymphomas were categorized entirely by their cytologic and architectural properties. The surgical pathologist's

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interpretation was rarely challenged. Recognition of the immunologic properties of non-Hodgkin's lymphoma led to revisions in lymphoma classification in the 1970's. Competing nosologies (Lukes and Collins, Lennert (Kiel), and Berard and Jaffe) all had pockets of acceptance (based largely on geography or training lineage) – but none was universally recognized. Clinicians became frustrated by the discordant terms (e.g. "large non-cleaved cell, small cleaved cell" vs. "centroblast", "centrocyte"). Pathologists found it difficult to master the different systems, and often adopted only one (with frequent referral to the Rappaport classification in the pathology report as a fallback.) Increasingly, immunologic studies (not widely available at that time) played a role in the final interpretation of the lymphoma. In 1982, the National Cancer Institute pushed for a consensus conference to reconcile the differences. No consensus could be reached, but a "Working Formulation" was adopted which created 3 basic prognostic categories for clinicians, and restored the power of the microscope in lymphoma interpretation for pathologists. Everyone was happy, except a group of hematopathologists, who felt the Working Formulation was an oversimplification and did not permit accurate classification of newly recognized entities such as mantle zone lymphoma or anaplastic large cell lymphoma. In 1994, this International Lymphoma Study Group proposed the "Revised European-American Lymphoma" (REAL) classification, incorporating clinical behavior, histology, immunology, cytogenetic and molecular genetic findings. This classification has proved to be relatively reproducible and has been widely adopted by pathologists and oncologists. (Advances in immunophenotypic methods, which allow greater applicability, have aided this acceptance.) The same group of hematopathologists recently collaborated with a large group of hematologists, oncologists and general pathologists to produce a World Health Organization classification, which expands the REAL classification (and now includes all lymphoid, myeloid, and histiocytic/dendritic cell neoplasms). The results are well presented in a new WHO "blue book" edited by Elaine Jaffe and others – *Pathology & Genetics of Tumours of the Haematopoietic and Lymphoid Tissues* (IARC Press, $75.00 – I call that a bargain). An order form can be downloaded from http://www.iarc.fr/. I would highly recommend this book to anyone interested in a relatively inexpensive, comprehensive, authoritative, and well illustrated reference. For those unfamiliar with some of the more recently described lymphomas, buy this book and you won't get fooled again. (At least not for a while.)

John D. Benson, MD

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1. Higby, DJ. A Practical Classification of Lymphoma (correspondence). *N Engl J Med* 1979; 300:1283.

2. Banks PM. The New WHO Classification of Malignant Lymphomas. The Walter R. Benson Pathology Lecture, UNC School of Medicine, April 20, 2002.

Dr. Peter Banks is the Director of Hematopathology at Carolinas Medical Center and was one of the 18 hematopathologists participating in the International Lymphoma Study Group discussed above. I am grateful that he agreed to give the first lecture named in honor of my father, the former Chief of Surgical Pathology at UNC Medical School.

For further information, call the Laboratory (784-3040). Telephone extensions are: Pathologists' Direct Line (3201), Sharon Logue (Lab Director 2400), Robin Ivosic (Microbiology Lab Manager 3053), Elaine Patterson (Core Lab Manager 3054), Jackie Okoth (Core Lab PM Manager 4248), Diane Young (Anatomic Pathology Manager 3888), Nga Moore (Customer Service Manager 3396)

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